ACP JOURNAL CLUB

EVIDENCE-BASED MEDICINE FOR BETTER PATIENT CARE

JULY/AUGUST 2007 • VOLUME 147, NUMBER 1

PUBLISHED BY THE AMERICAN COLLEGE OF PHYSICIANS

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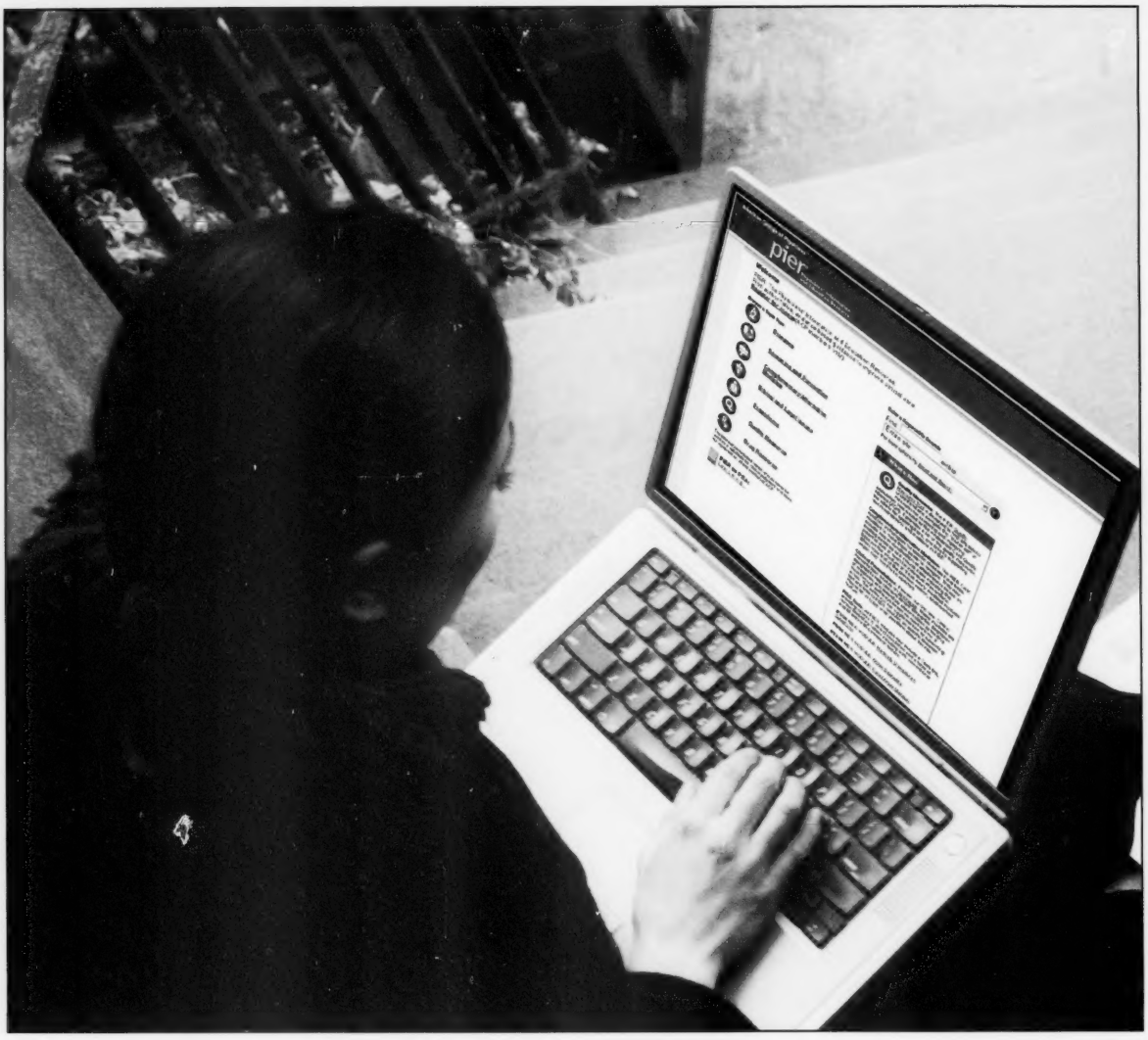

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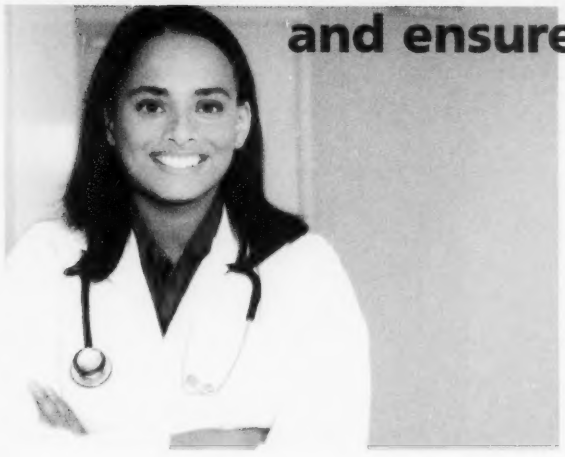

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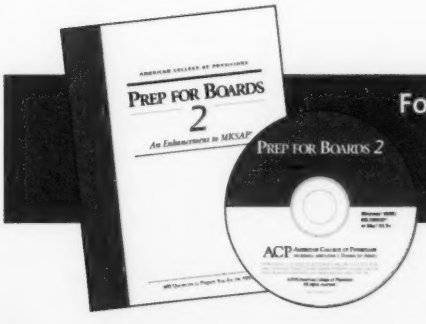

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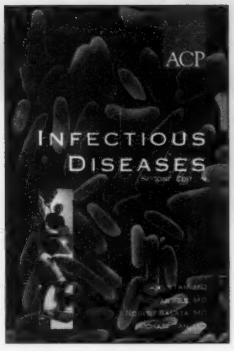

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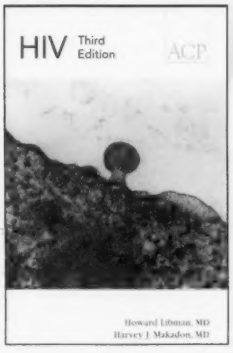

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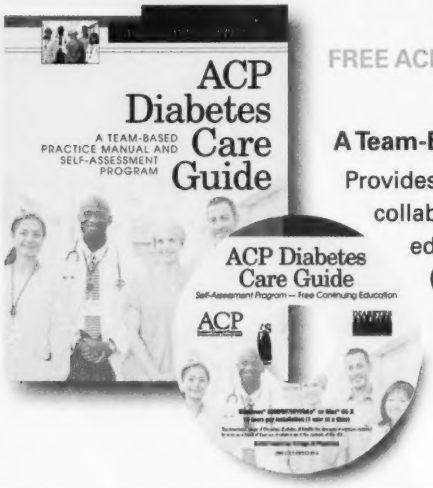

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Ann Intern Med. 2007;146:233-43 2

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JAMA. 2007;297:842-57 4

Exercise program for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial. Rolland Y, Pillard F, Klapouszczak A, et al.
J Am Geriatr Soc. 2007;55:158-65 5

Systematic review: the value of the periodic health evaluation. Boulware LE, Marinopoulos S, Phillips KA, et al.
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Clinical and economic impact of stress echocardiography compared with exercise electrocardiography in patients with suspected acute coronary syndrome but negative troponin: a prospective randomized controlled study. Jeetley P, Burden L, Stoykova B, Senior R.
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* Approximately 60 journals from other areas of health care are also reviewed. This list is available on request from McMaster University (address appears on page A-2).

Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials. Wijeysundera HC, Vijayaraghavan R, Nallamothu BK, et al. 11
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Optimal medical therapy with or without PCI for stable coronary disease. Boden WE, O'Rourke RA, Teo KK, et al.
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Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents. Kastrati A, Mehilli J, Pache J, et al.
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The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Dube C, Rostom A, Lewin G, et al.
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Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Gebski V, Burmeister B, Smithers BM, et al.
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Risk of subsequent fracture after low-trauma fracture in men and women. Center JR, Bliuc D, Nguyen TV, Eisman JA.
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2. *Citation for material taken from a structured abstract, written without attribution by a staff member*: Tissue-plasminogen activator reduced mortality rates compared with streptokinase for acute myocardial infarction [Abstract]. ACP J Club. 1997 Jan-Feb;126:3. Abstract of: Califf RM, White HD, Van de Werf F, et al., for the GUSTO-I Investigators. One-year results from the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I) Trial. Circulation. 1996 Sep 15;94:1233-8.
3. *Citation for material taken from a commentary to an article*: Meisner JS. Diastolic dysfunction was predictive of all-cause mortality [Comment]. ACP J Club. 2003 Sep-Oct;139:53.
4. *Citation for material taken from a letter*: Peterson D. Numbers needed to treat derived from meta-analysis: a word of caution [Letter]. ACP J Club. 2003 Jul-Aug;139:A15; author reply A15.

Improving Journal Club Presentations, or, I can present that paper in under 10 minutes

Fifteen years ago we sought a method for teaching residents how to make lean, pithy journal club presentations. Our aim was to help them distill an article down to its core while systematically reviewing its validity and telling a compelling story. Others have created successful journal clubs by explicitly linking the educational experience to questions raised in caring for patients (1).

Brief article presentations are structurally similar to the brief case presentations we do all the time. On work rounds, morning report, or sign-out, the goal is to communicate the essential information about a patient in a concise, mostly standardized format that is easily digested by the listener. We reasoned that, just as learners progress from meandering and imprecise case presentations on clinical clerkships to brief, utilitarian sign-outs as senior residents, journal club presenters can learn to efficiently convey the essence of an article.

We introduce this model of journal club presentation to medical residents in a small-group workshop early during internship and then deepen residents' skills during our clinical epidemiology course in the second year (2). Residents' skills are reinforced and refined throughout residency at a weekly journal club attended by 10 to 20 residents, fellows, and faculty.

We use the following 10-step guideline to help presenters increase efficiency in assessing a study's validity and results and to increase confidence in limiting a presentation to the core essentials. Faculty members model the process, and residents learn through reflective practice.

1. Describe the case or problem that attracted you to this paper.

Start your article presentation with a brief case presentation, or briefly explain how the article is relevant to a patient or problem you are considering. This helps listeners more fully engage with your presentation and makes it more of a story.

For example, *"An otherwise-healthy 68 year-old man came to see me after he suffered a transient ischemic attack [TIA], and I wondered if he should be on a statin even though his risk for cardiac disease was low."*

2. Explain how you came across this article.

Very briefly describe the search strategy you used to track down this particular article.

"I found this paper by searching Medline using the terms Cerebrovascular Accident, Hydroxymethylglutaryl-CoA Reductase Inhibitors, and the Clinical Query for therapy (maximizing specificity) which identified 9 articles."

3A. Describe the study.

In a case presentation we start with some standard descriptors of the patient followed by the chief complaint or statement of the clinical problem. For example: *"This is a 55 y/o male smoker from Bangladesh who presented within 2 hours of burning chest pain and is admitted as a rule out."*

When presenting an article we can think of some standard descriptors. Here are some examples: What type of question was asked (e.g., diagnostic, therapeutic, prognostic, etiologic, or economic)? What type of study (method) was used (e.g., randomized controlled trial [RCT], retrospective cohort, case-control, meta-analysis, cross-sectional, descriptive, decision analytic, or cost-effectiveness)? Where was the study done (if relevant) (e.g., multicenter, Veterans' Affairs [VA], population-based, Antarctica, NYC, academic medical center, subspecialty clinic)? Are there any other outstanding features (well-known author, first of its kind)?

So we might start by saying *"This was a multinational, randomized, controlled trial of therapy, and the first study designed to answer the question ..."*

3B. Describe the research question.

The chief complaint of an article is the research question or hypothesis to be tested. A well-built research question has 4 basic components (PICO) (3):

Population: Who was studied?

Intervention (or exposure): What therapy, risk factor, tests?

Comparison or control: What alternative to intervention or exposure?

Outcome: Clinical, functional, economic?

"Over a 5-year period, does high-dose atorvastatin reduce the incidence of stroke among patients with recent stroke or TIA who have no known coronary heart disease?" (4)

4. State the importance/relevance/context of the question.

Following this 1-line description of the study and statement of the question, concisely state the importance of the question. This information can usually be found in the introduction, where the authors put their study in the context of other literature. This can be described in 1 to 3 sentences.

"Therapy with statins reduces the risk for stroke among patients with coronary heart disease and those at increased risk for cardiovascular [CV] disease. No studies thus far, however, show that statin treatment decreases the risk for recurrent stroke among otherwise-healthy patients with a history of stroke or TIA."

5. Describe the methods by giving more detail on the components of the question.

Following this brief background, 1 way of briefly describing the methods is to give slightly more detail on the Patients, Intervention, Comparison, and Outcomes (PICO) related to the question:

P: *"The study included 4371 patients, 60% men with an average age of 63 years and mean low-density-lipoprotein (LDL) cholesterol of 133 mg/dL. All patients had a recent stroke (69%) or TIA (31%). Those with atrial fibrillation, embolism from other cardiac sources, and subarachnoid hemorrhage were excluded."*

IC: *"Atorvastatin 80 mg daily or identical placebo."*

O: *"After a median of 4.9 years of follow up, the primary outcome was incidence of fatal or nonfatal stroke, and all-cause death. Secondary endpoints included a composite endpoint of stroke or TIA, major coronary event, major CV event, acute coronary event, any coronary event, revascularization, and any CV event."*

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THERAPEUTICS

Review: Lifestyle or pharmacologic interventions prevent or delay type 2 diabetes in impaired glucose tolerance

Gillies CL, Abrams KR, Lambert PC, et al. **Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis.** BMJ. 2007;334:299.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Endocrinology ★★★★★★☆

QUESTION

In persons with impaired glucose tolerance, do lifestyle or pharmacologic interventions prevent or delay type 2 diabetes mellitus (DM)?

METHODS

Data sources: MEDLINE (1966 to July 2006), EMBASE/Excerpta Medica (1980 to July 2006), Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews (Issue 2, 2006), references of relevant articles, and experts in the field.

Study selection and assessment: Randomized controlled trials (RCTs) that evaluated an intervention to delay or prevent type 2 DM in persons with impaired glucose tolerance and had an outcome measurement of diabetes. 21 RCTs met the selection criteria, and 17 RCTs (n = 8084, mean age range 39 to 57 y, mean body mass index range 24 to 36 kg/m^2, average follow-up range 0.4 to 4.6 y) were included in the meta-analysis. Among the 17 RCTs, 8 had quality scores ≥ 3 out of 5 on the Jadad scale, and 2 had allocation concealment.

Outcomes: Development of type 2 DM and adverse events.

MAIN RESULTS

Meta-analysis using a random-effects model showed that both lifestyle interventions (diet, exercise, or both) and pharmacologic interventions (oral diabetes drugs [acarbose, flumamine, glipizide, metformin, or phenformin] or an antiobesity drug [orlistat]) reduced the incidence of type 2 DM (Table); 2 RCTs assessing troglitazone were excluded from the meta-analysis because the drug had been removed from several markets worldwide because of liver toxicity. In 1 RCT, jiangtang bushen (a Chinese herb) did not reduce DM (Table). Adverse events related to the pharmacologic interventions (gastrointestinal and hypoglycemic symptoms) were more common in the treatment groups (no statistical tests reported).

CONCLUSION

In people with impaired glucose tolerance, lifestyle or pharmacologic interventions prevent or delay type 2 diabetes mellitus.

Source of funding: UK Medical Research Council and Economic and Social Research Council.

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Lifestyle or pharmacologic interventions vs placebo to prevent or delay type 2 diabetes mellitus in persons with impaired glucose tolerance at mean follow-up range 0.4 to 4.6 y*

Outcome	Comparisons	Number of trials (n†)	Hazard ratio (95% CI)	NNT (credible interval)
Type 2 diabetes mellitus	Lifestyle vs placebo‡	10 (4452)	0.51 (0.44 to 0.60)	7 (5 to 9)
	Oral diabetes drug vs placebo§	8 (4580)	0.70 (0.62 to 0.79)	11 (9 to 15)
	Orlistat vs placebo	2 (814)	0.44 (0.28 to 0.69)	6 (5 to 8)
	Jiangtang bushen vs placebo	1 (51)	0.32 (0.03 to 3.07)	Not significant

*Abbreviations defined in Glossary.
†Sample sizes provided by author.
‡Lifestyle interventions included diet, exercise, or both.
§Oral diabetes drugs were acarbose, flumamine, glipizide, metformin, or phenformin.

COMMENTARY

The systematic review by Gillies and colleagues provides pooled estimates of effectiveness of pharmacologic and lifestyle interventions in preventing type 2 DM in persons with impaired glucose tolerance. Lifestyle (diet, exercise, or both) interventions reduced progression to type 2 DM by 50% and were at least as effective as drugs.

Sustained effects from preventive interventions are clinically important. For instance, rosiglitazone (RG) has been associated with a 60% reduction in progression to type 2 DM in the DREAM trial (1). However, the unpublished washout data suggest a similar incidence of type 2 DM in RG and placebo-treated groups soon after discontinuation of RG (2). Other drugs have also been reported to lack sustained diabetes prevention properties after washout (3). On the other hand, sustained effects have been reported from intensive lifestyle interventions (4). Drugs used in type 2 DM prevention trials are also more commonly associated with side effects (e.g., gastrointestinal upset, liver function decline, and hypoglycemia) than lifestyle interventions. RG has been associated with weight gain, excess fractures, and a 7-fold incidence of nonfatal heart failure (1, 2).

Cost, adverse effects, and nonsustained efficacy associated with diabetes prevention drugs suggest that lifestyle interventions remain the mainstay of diabetes prevention.

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Intensive insulin therapy during cardiac surgery did not reduce mortality or morbidity but increased risk for stroke

Gandhi GY, Nuttall GA, Abel MD, et al. **Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial.** Ann Intern Med. 2007;146:233-43.

Clinical impact ratings: Cardiology ★★★★★☆☆ Endocrinology ★★★★★★☆

QUESTION

In patients having cardiac surgery, does intraoperative intensive insulin therapy (IIT) reduce morbidity and mortality?

METHODS

Design: Randomized controlled trial (RCT).
Allocation: Concealed.*
Blinding: Blinded (outcome assessors).*
Follow-up period: 30 days.
Setting: A tertiary care teaching hospital in Rochester, Minnesota, USA.
Patients: 400 patients (mean age 63 y, 68% men, 96% white) who were having elective cardiac surgery. Patients having off-pump cardiopulmonary bypass procedures were excluded.
Intervention: IIT (n = 199) or conventional insulin therapy (n = 201) during surgery. IIT consisted of continuous intravenous (IV) insulin infusion when blood glucose levels were > 5.6 mmol/L (> 100 mg/dL) and then adjustment to maintain intraoperative glucose levels at 4.4 (80 mg/dL) to 5.6 mmol/L (100 mg/dL). The conventional-therapy group was given insulin during surgery only when glucose levels were ≥ 11.1 mmol/L (≥ 200 mg/dL). After surgery, both groups received IV insulin infusion to maintain normal blood glucose levels.
Outcomes: A composite endpoint of death, sternal infections, prolonged (> 24 h) pulmonary ventilation, new-onset atrial fibrillation, heart block requiring permanent pacemaker, cardiac arrest, stroke, or acute renal failure within 30 days of surgery. Secondary outcomes were length of stay in the intensive care unit (ICU) and hospital. The study had 90% power to detect a 40% decrease in the composite endpoint.
Patient follow-up: 93% (intention-to-treat analysis).

MAIN RESULTS

Groups did not differ for the primary composite endpoint (Table) or for ICU or hospital length of stay. The IIT group had a higher incidence of stroke and nonsignificant increases in the incidences of death and heart block requiring pacemaker than did the conventional-therapy group (Table).

CONCLUSION

Intensive insulin therapy during cardiac surgery did not reduce morbidity and mortality but increased risk for stroke more than conventional insulin therapy.

Sources of funding: Novo Nordisk and Mayo Foundation.

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*See Glossary.

Intensive insulin vs conventional insulin therapy during cardiac surgery at 30 days†

Outcomes	Intensive insulin	Conventional therapy	RRR (95% CI)	NNT
Composite endpoint‡	44% (82/185)	46% (86/186)	4.1% (–20 to 23)	Not significant
			RRI (CI)	NNH (CI)
Stroke	4.3% (8/185)	0.54% (1/186)	704% (33 to 4832)	27 (13 to 120)
Death	2.2% (4/185)	0% (0/186)	—	Not significant
Heart block requiring pacemaker	2.7% (5/185)	0.54% (1/186)	403% (–21 to 3131)	Not significant

†Abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from data in article.
‡Death, sternal infections (3.2% vs 3.8%), pulmonary ventilation for > 24 hours (19% vs 20%), new-onset atrial fibrillation (29% vs 32%), heart block requiring pacemaker, cardiac arrest (0.54% vs 0%), stroke, or acute renal failure (3.2% vs 2.2%).

COMMENTARY

The landmark study by Van den Berghe and colleagues showed that postoperative IIT reduced mortality and morbidity in patients in the surgical ICU (1). In another study, patients in the medical ICU treated with IIT had reduced morbidity, and a subgroup of patients in the ICU ≥ 3 days had reduced morbidity and mortality (2).

It is tempting to extrapolate results from these trials to other settings. Because intraoperative hyperglycemia was found to be a marker for complications in a previous observational study (3), it was hypothesized that maintaining intraoperative normoglycemia could reduce complications. Surprisingly, the RCT by Gandhi and colleagues failed to show any benefit.

There are several potential explanations. First, if there is a benefit to intraoperative IIT, it may be < 40% of the difference the study was powered to detect. Second, it is possible that the benefit of intensive glycemic control is realized after prolonged postoperative insulin therapy and not after a few hours of intraoperative insulin. Third, although the probability is relatively small, the findings might have occurred by chance. The unexpected potential harms, an increased risk for stroke and a trend toward increased death in the IIT group, are of concern. If the risk is real, the mechanism is unclear, as episodes of hypoglycemia did not differ between groups.

For internists and endocrinologists, the study by Gandhi and colleagues does not affect practice. For cardiothoracic surgeons and anesthesiologists, given the lack of supporting data and extensive resources required to implement IIT protocols during surgery, intraoperative IIT is not ready for current use.

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An intensive smoking cessation intervention reduced mortality in high-risk smokers with cardiovascular disease

Mohiuddin SM, Mooss AN, Hunter CB, et al. **Intensive smoking cessation intervention reduces mortality in high-risk smokers with cardiovascular disease.** Chest. 2007;131:446-52.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Hospitalists ★★★★★★☆ Cardiology ★★★★★☆☆ Pulmonology ★★★★★★☆

QUESTION

In high-risk smokers hospitalized for cardiovascular disease, does an intensive behavioral plus pharmacotherapy smoking cessation intervention after discharge plus usual care reduce mortality and hospital admissions more than usual care alone?

METHODS

Design: Randomized controlled trial.
Allocation: {Not concealed}†.*
Blinding: Unblinded.*
Follow-up period: 2 years.
Setting: Coronary care unit in a university hospital in Nebraska, USA.
Patients: 209 patients 30 to 75 years of age (mean age 55 y, 63% men) who were admitted to the coronary care unit with the acute coronary syndrome or decompensated heart failure, had smoked for ≥ 5 years, and had a Fagerstrom score > 7. Exclusion criteria included current alcohol or illicit substance addiction.
Intervention: Intensive smoking cessation intervention plus usual care (n = 109) or usual care only (n = 100). The intensive intervention included weekly 60-minute counseling sessions for ≥ 3 months after discharge and individualized nicotine replacement therapy and/or bupropion at no cost. Intervention-group patients were re-treated if they started smoking again. Usual care included written self-help materials and a 30-minute counseling session before discharge.
Outcomes: Point prevalence (no smoking since the previous follow-up visit) and continuous abstinence (no smoking since the first follow-up visit) quit rates (both confirmed by measurement of expired carbon monoxide), mortality, and hospital admission.
Patient follow-up: 96% (intention-to-treat analysis).

MAIN RESULTS

The intensive-intervention group had higher quit rates than the usual-care group throughout the follow-up period and at 2 years (Table). The intensive intervention led to fewer hospital admissions and lower all-cause mortality (Table).

CONCLUSION

In high-risk smokers hospitalized with cardiovascular disease, an intensive smoking cessation intervention reduced hospital admissions and all-cause mortality more than usual care only.

Source of funding: State of Nebraska Cancer and Smoking Disease Research fund.

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*See Glossary.

†Information provided by author.

Intensive smoking cessation intervention plus usual care vs usual care only in high-risk smokers hospitalized for cardiovascular disease at 2 years‡

Outcomes	Intensive intervention plus usual care	Usual care only	RBI (95% CI)	NNT (CI)
Point prevalence quit rate	39%	9%	338% (132 to 752)	4 (3 to 6)
Continuous abstinence quit rate	33%	9%	267% (91 to 621)	5 (3 to 8)
			RRR (CI)	
All-cause mortality	2.8%	12%	77% (27 to 93)	11 (6 to 41)
Cardiovascular mortality	2.8%	9%	69% (–1.1 to 91)	Not significant
All-cause hospital admissions	23%	41%	44% (16 to 63)	6 (4 to 19)
Cardiovascular hospital admissions	18%	37%	50% (21 to 69)	6 (4 to 16)

‡Abbreviations defined in Glossary. RBI, RRR, NNT, and CI calculated from data in article.

COMMENTARY

This small but well-designed clinical trial by Mohiuddin and colleagues found that a smoking cessation program increased quit rates and reduced hospitalizations and mortality in high-risk cardiac patients. Several aspects of the cessation intervention deserve comment. First, although the Joint Commission on Accreditation of Healthcare Organizations quality initiatives encourage U.S. hospitals to identify and intervene in smokers admitted with acute cardiac syndromes, few provide the 30-minute inpatient counseling session described here. Second, the intervention included weekly counseling for 3 months after discharge. Outpatient counseling is unavailable or not covered for most Americans. In 2005, only 14 states covered cessation counseling for all Medicaid recipients and only 1 state (Oregon) covered all forms of counseling and medication (1). Third, medications, which probably doubled quit rates (2), were provided to patients free of charge, and 75% of patients in the intervention group took advantage of them. Fourth, multiple opportunities for re-treatment were allowed. We know that tobacco dependence is a chronic, relapsing condition, and > 25% of the intervention group were re-treated during the study period.

This landmark study calls to mind the first study of lipid lowering that showed a significant reduction in mortality and forever changed clinical practice (3). Even if we ignore the effect on mortality, the costs to identify and intervene in smokers are minimal compared with hospitalization costs. The study should serve as a call to all payers, public and private, to reevaluate their coverage for intensive tobacco cessation interventions. Physicians need to advocate for increasing coverage and decreasing barriers to effective smoking cessation treatments.

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Review: Antioxidant supplements for primary and secondary prevention do not decrease mortality

Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. **Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis.** JAMA. 2007;297:842-57.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Cardiology ★★★★★★☆ Endocrinology ★★★★★★☆ Gastroenterology ★★★★★★☆ Geriatrics ★★★★★☆☆ Nephrology ★★★★★★☆ Neurology ★★★★★☆☆ Oncology ★★★★★★☆ Rheumatology ★★★★★★☆ Dermatology ★★★★★★☆

QUESTION

In healthy people or patients with chronic diseases, do antioxidant supplements (ASs) decrease mortality?

METHODS

Data sources: MEDLINE (1966 to October 2005), EMBASE/Excerpta Medica (1985 to October 2005), Cochrane Central Register of Controlled Trials (Issue 3, 2005), Science Citation Index Expanded (1945 to October 2005), and bibliographies of relevant studies.

Study selection and assessment: Randomized controlled trials (RCTs) that compared ASs (β-carotene; vitamin A, C, or E; or selenium, separately or in combination) with placebo or no intervention in healthy adults or patients with chronic diseases. Trials on acute, infectious, or malignant diseases except for nonmelanoma skin cancer were excluded. 68 RCTs (n = 232 606, mean age 62 y, mean 45% women in 63 RCTs, follow-up range 28 d to 14 y [median 2 y]) met the selection criteria. Among them, 47 (n = 68 167) were secondary prevention trials and included patients with gastrointestinal, cardiovascular, neurologic, ocular, dermatologic, rheumatoid, renal, cardiovascular, endocrinologic, or unspecified diseases. All ASs were administered orally: β-carotene 1.2 to 50 mg (mean 18 mg), vitamin A 1333 to 200 000 IU (mean 20 219 IU), vitamin C 60 to 2000 mg (mean 488 mg), vitamin E 10 to 5000 IU (mean 569 IU), and selenium 20 to 200 μg (mean 99 μg) daily or on alternate days for a period of 28 days to 12 years (mean 2.7 y). 47 RCTs (n = 180 938) had high methodological quality that was defined as adequate randomization, allocation concealment, blinding, and follow-up.

Outcomes: Mortality.

MAIN RESULTS

Meta-analysis of 68 RCTs showed that groups did not differ for mortality (Table). Meta-analysis of 47 high-quality RCTs showed that ASs increased mortality, while meta-analysis of 21 low-quality RCTs showed that ASs decreased mortality (borderline significance) (Table). Subgroup analysis of high-quality RCTs (excluding selenium trials) showed that β-carotene (RR 1.07, CI 1.02 to 1.11), vitamin A (RR 1.16, CI 1.10 to 1.24), or vitamin E (RR 1.04, CI 1.01 to 1.07), alone or combined, increased mortality. Subgroup analysis also showed that vitamin C or selenium had no significant effect on mortality.

CONCLUSION

In healthy people or patients with chronic diseases, antioxidant supplements do not decrease mortality.

Source of funding: Copenhagen Trial Unit, Copenhagen University Hospital.

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Antioxidant supplements (β-carotene; vitamin A, C, or E; or selenium, separately or in combination) vs placebo or no intervention in healthy adults or patients with chronic diseases*

Outcomes at median 2 years	Number of trials (n)	Weighted event rates		RRI (95% CI)	NNH (CI)
		Antioxidant supplements	Placebo or no intervention		
Mortality in all included RCTs	68 (232 606)	11%	11%	2% (–2 to 6)	Not significant
Mortality in high-quality RCTs	47 (180 938)	12%	11%	5% (2 to 8)	180 (112 to 449)
				RRR (CI)	NNT (CI)
Mortality in low-quality RCTs	21 (51 668)	6.4%	7.0%	9% (0 to 17)	160 (85 to ∞)

*Abbreviations defined in Glossary. Weighted event rates, RRI, RRR, NNT, NNH, and CI calculated from data in article using a random-effects model.

COMMENTARY

ASs are used by a large segment of the population. Hence, the review by Bjelakovic and colleagues has major implications for public health. More relevant than the overall analysis that combined chemically diverse antioxidants (including combinations) in diverse settings, the agent-specific analyses suggest that β-carotene, vitamin A, or vitamin E, alone or combined, increase mortality, whereas vitamin C or selenium has no effect. The results are believable because of the careful, prespecified protocol, comprehensive sensitivity analyses, and precise confidence limits.

2 other features of the review lend further support to the findings. First, signals of increased mortality were even more prominent in methodologically strong trials characterized as being at low risk for bias. Second, causality was strengthened by significant dose-response gradients for several of the antioxidants.

Given the number of persons exposed to these agents, this review suggests that several thousand deaths each year may result from use of ASs, which have hitherto been considered by many physicians to be benign or even beneficial compounds. The public perception that vitamins and other antioxidants have favorable health effects because they are "natural" rather than pharmacologic is clearly wrong and in light of this review must be corrected by clinicians and other health advocates.

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An exercise program led to a slower decline in activities of daily living in nursing-home patients with Alzheimer disease

Rolland Y, Pillard F, Klapouszczak A, et al. **Exercise program for nursing home residents with Alzheimer's disease: a 1-year randomized, controlled trial.** J Am Geriatr Soc. 2007;55:158-65.

Clinical impact ratings: Geriatrics ★★★★★★☆ Neurology ★★★★★☆☆ Phys Med & Rehab ★★★★★★☆

QUESTION

In patients with Alzheimer disease (AD) in nursing homes, does an exercise program slow the decline in ability to do activities of daily of living (ADLs)?

METHODS

Design: Randomized controlled trial.
Allocation: Concealed.*
Blinding: Blinded (outcome assessors and {data analysts}†).*
Follow-up period: 12 months.
Setting: 5 nursing homes in Toulouse, France.
Patients: 134 patients who were 62 to 103 years of age (mean age 83 y, 75% women), met the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer Disease and Related Disorders Association criteria for probable or possible AD, had lived in the nursing home for ≥ 2 months, and were able to transfer from a chair and walk ≥ 6 meters without human assistance. Exclusion criteria were vascular dementia or Parkinson disease, surgery in the coming year, cardiac condition that could worsen with exercise, or terminal illness with life expectancy < 6 months.
Intervention: Exercise (n = 67) or routine medical care (n = 67). Patients in the exercise group were divided into small groups of 2 to 7 (mean 5) patients according to physical, cognitive, and behavioral performance. The exercise program was individualized and included aerobic, strength, flexibility, and balance training. At least half of each session consisted of walking. The sessions were held for 1 hour in the afternoon twice a week, with ≥ 2 days between exercise sessions.
Outcomes: Decline from baseline in Katz ADL score (range 0 [dependent] to 6 [independent]).
Patient follow-up: 82% (100% included in the intention-to-treat analysis).

MAIN RESULTS

At 12 months, patients in the exercise group showed less decline in performance of ADLs than did patients in the routine medical care group (Table). Exercise and routine medical care did not differ for number of falls (139 vs 136), fractures (5 vs 2), or deaths (7 vs 8).

CONCLUSION

In nursing-home patients with Alzheimer disease, an exercise program led to a slower decline in the ability to do activities of daily living.

Sources of funding: Caisse Nationale d'Assurance Maladie et du Travail and University Hospital of Toulouse.

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*See Glossary.
†Information provided by author.

Exercise vs routine medical care for patients with Alzheimer disease in nursing homes‡

Outcomes at 12 mo	Mean score decrease from baseline		Difference in mean score decrease	P value
	Exercise	Routine medical care		
Katz ADL score§	0.6	0.9	0.3	0.02

‡ADL = activities of daily living.
§High score = more independent.

COMMENTARY

The cholinesterase inhibitor donepezil significantly slows decline in ADLs in nursing-home patients with severe AD (1). Exercise also may slow ADL loss through relative preservation of cognitive function rather than through improvement of physical performance. Rolland and colleagues found no statistically significant differences between the exercise and control groups in the change scores for individual ADLs, suggesting that the differential decline in overall ADL function was not driven by differences in physical performance. Several large-scale cohort studies have shown less cognitive decline in older persons with high activity compared with those with low physical activity (2). After 5 years of follow-up in the Canadian Study of Health and Aging, the most active participants were 50% less likely to develop AD and 37% less likely to develop any form of cognitive impairment than the least active participants (3). The mechanism by which exercise retards cognitive decline is unknown.

In the present study, patients assigned to a moderate, twice-weekly exercise program experienced less decline in ADLs than the usual-care group, although one third of the patients attended fewer than one third of the sessions. Post hoc analysis showed that the amount of decline was inversely correlated with the number of sessions attended. The relative risk reduction (RRR) for ADL loss at 1 year in the exercise group was 33%. This compares favorably with an RRR of 48% for ADL loss in nursing-home patients with advanced AD randomized to donepezil or placebo for 6 months (1). Although the absolute risk reduction for the exercise group was small, the study did not address the effect of this difference on staff effort. Even small reductions in ADL independence can translate into significant increases in the time required by staff to assist patients.

While this study did not address cost-effectiveness, implementing a structured exercise program for nursing-home patients with severe dementia may be cost-effective when compared with cholinesterase inhibitors, particularly once staff time and the cost and potential side effects of cholinesterase inhibitors are factored into the analysis.

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Review: Periodic health examination increases delivery of some clinical preventive services and reduces patient worry

Boulware LE, Marinopoulos S, Phillips KA, et al. **Systematic review: the value of the periodic health evaluation.** Ann Intern Med. 2007;146:289-300.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Public Health ★★★★☆☆☆

QUESTION

In adults, is the periodic health evaluation (PHE) beneficial in terms of delivering preventive services, improving clinical outcomes, and reducing health care costs?

METHODS

Data sources: MEDLINE, the Cochrane Library, Health Technology Assessment Database, National Health System Economic Evaluation Database, and Cumulative Index of Nursing and Allied Health Literature (to September 2006); hand-searches of 24 general medicine, preventive medicine, and public health periodicals; and reference lists.

Study selection and assessment: English-language randomized controlled trials (RCTs) and observational studies that evaluated the benefits and harms of the PHE compared with usual care in adults. PHE was defined as ≥ 1 visit with a health care provider for the primary purpose of assessing the patient's overall health and risk factors for preventable disease. It consists only of the relevant history-taking, risk assessments, and physical examinations that could lead to delivering preventive services. 10 RCTs and 23 observational studies met the selection criteria, but only the 21 studies (10 RCTs, 2 cohort studies, and 9 cross-sectional studies) that were considered to provide "best available evidence" (according to the Grading of Recommendations, Assessment, Development, and Evaluation [GRADE] classification scheme) were included in the analyses.

Outcomes: Delivery of clinical preventive services, short-term clinical outcomes, and long-term clinical outcomes and costs.

MAIN RESULTS

The strength and consistency of the evidence varied widely across outcomes, and the magnitude and even the direction of the treatment effect varied within some outcomes. The PHE showed benefit in increasing use of the gynecologic examination or Papanicolaou smear, cholesterol screening, and colon cancer screening and decreasing patient worry (Table). The effect of the PHE on other outcomes, including costs, was mixed (Table).

CONCLUSION

In adults, the periodic health examination shows benefit over usual care through increased delivery of some recommended clinical preventive services and reduced patient worry.

Source of funding: Agency for Healthcare Research and Quality.

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Effect of the periodic health examination (PHE) vs usual care on delivery of clinical preventive services, clinical outcomes, and health care costs in adults

Outcome categories	Specific outcomes	Number and type of studies*	Quality of evidence	Direction (magnitude) of effect†
Delivery of preventive services	Gynecologic examination/ Papanicolaou smear	2 RCTs	High	Beneficial (small to large)
	Counseling	1 RCT, 6 Obs	Low	Mixed
	Immunizations	3 RCTs	Medium	Mixed
	Cholesterol screening	1 RCT, 4 Obs	Medium	Beneficial (small to large)
	Colon cancer screening	2 RCTs	High	Beneficial (large)
	Mammography	1 RCT, 1 Obs	Low	Mixed
Short-term clinical endpoints	Disease detection	2 RCTs	Medium	Mixed
	Health habits	5 RCTs	Medium	Mixed
	Patient worry	1 RCT	Medium	Beneficial
	Health status	2 RCTs	Medium	Mixed
	Blood pressure	2 RCTs	High	Mixed
	Serum cholesterol	1 RCT, 1 Obs	Low	Mixed
	Body mass index	3 RCTs	Medium	Mixed
Long-term economic and clinical endpoints	Costs	4 RCTs	Medium	Mixed
	Disability	2 RCTs	Medium	Mixed
	Hospitalization	3 RCTs	High	Mixed
	Mortality	5 RCTs	Medium	Mixed

*RCT = randomized controlled trial; obs = observational study.

†Beneficial = all studies showed a benefit of PHE over usual care; mixed = some studies showed a benefit of PHE, but others showed harm or a neutral effect.

COMMENTARY

The review by Boulware and colleagues touched on 2 central questions in preventive health care. First, does each individual component of the PHE (such as Papanicolaou smear or blood pressure measurement), if actually done and coupled with follow-up care, improve health outcomes? Second, does providing preventive health care during periodic visits for that purpose alone (variously called health maintenance visits or, misleadingly, "annual physicals") produce higher rates of preventive care than adding this agenda to visits for acute and chronic illness?

Unfortunately, this review mixed the 2 questions and thus was limited in what it could accomplish. As the authors pointed out, the included studies were characterized by "complexity and heterogeneity." Several studies were done in the 1960s and 1970s, before most evidence for the effectiveness of preventive care was available. Component studies included different screening tests, immunizations, and behavioral interventions and assessed different outcomes over different follow-up periods. Thus, the review could have failed to detect preventive care that is actually effective. Even so, the review supports some practices: gynecologic examinations and Papanicolaou smears, cholesterol screening, and fecal occult blood testing.

In practice, clinicians should include in their preventive efforts only those components with strong evidence for efficacy. Several organizations, such as the U.S. Preventive Services Task Force and the Canadian Task Force on Preventive Health Care, provide rigorous reviews of the evidence and recommendations. As for how preventive care should be delivered, clinicians are free to choose any way that works in their setting. But they should understand that preventive care is usually more complete when offered during periodic evaluations rather than as part of usual care (1) and when it involves systems and teamwork. Of course, periodic evaluations only work for patients who come in for them. For those who do not, opportunistic prevention is better than nothing.

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Review: Flight times > 8 hours and the presence of risk factors for VTE increase travel-related VTE

Philbrick JT, Shumate R, Siadaty MS, Becker DM. **Air travel and venous thromboembolism: a systematic review.** J Gen Intern Med. 2007;22:107-14.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Hematol/Thrombo ★★★★★★☆ Trop & Travel Med ★★★★★☆☆

QUESTIONS

What are the risk factors for travel-related venous thromboembolism (VTE)? Which preventive treatments are effective?

METHODS

Data sources: MEDLINE (1966 to December 2005), Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, and bibliographies of relevant studies.

Study selection and assessment: Case–control or cohort studies and randomized controlled trials (RCTs) that evaluated any form of travel as a risk factor for VTE or preventive measures for travel-related VTE. Case reports, abstracts, and subgroup analyses of previously published studies were excluded. 25 studies met the selection criteria: 6 case–control studies (n = 207 to 988), 10 cohort studies (n = 320 to > 135 million), and 9 RCTs (n = 186 to 833); most studies evaluated air travel. The interventions evaluated in the 9 RCTs were low-molecular-weight heparin, aspirin, graduated compression stockings (12 to 30 mm Hg at the ankle), and herbal remedies with putative antithrombotic properties. Quality assessment of individual studies was based on 8 methodological criteria, which included adequate description of patient selection criteria, diagnosis, and treatment; equally matched comparison groups; and follow-up. 21 of 25 studies met ≥ 4 methodological criteria.

Outcomes: Incidence of VTE (pulmonary embolism, deep venous thrombosis [DVT], or both) after travel; associations between travel duration, clinical VTE risk, and travel-related VTE.

MAIN RESULTS

In RCTs and cohort studies evaluating air travel, the risk for asymptomatic VTE ranged from 0% to 12% and risk for symptomatic VTE was 27 per 1 million travelers. Multivariate logistic regression analysis showed that mean duration of air travel > 8 hours and high clinical risk for VTE (≥ 1 of previous DVT, prothrombotic blood disorder, body weight > 90 kg, limited mobility, cancer, or large varicose veins) increased risk for air-travel–related VTE (Table). In 9 studies (126 patients with VTE), additional risk factors were age > 40 years and use of female hormones. In 6 RCTs (n = 2482) evaluating air travel, use of compression stockings conferred a lower incidence of DVT than did no intervention (0.2% vs 3.7%, $P < 0.001$).

CONCLUSIONS

Mean duration of air travel > 8 hours and higher clinical venous thromboembolism risk increase risk for air-travel–related VTE. Graduated compression stockings are effective for preventing air-travel–related VTE.

Sources of funding: No external funding.

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Risk factors for travel-related venous thromboembolism (VTE)*

Risk factors	Odds ratio (95% CI)
Mean duration of air travel < 6 h	0.01 (0.002 to 0.11)
Mean duration of air travel 6 to 8 h	1.0
Mean duration of air travel > 8 h	2.3 (1.4 to 3.6)
Low clinical VTE risk†	1.0
High clinical VTE risk‡	3.6 (2.2 to 5.8)

*CI defined in Glossary. A multivariate logistic regression model was used.
†No known risk factors for VTE.
‡Previous deep venous thrombosis, prothrombotic blood disorder, body weight > 90 kg, limited mobility, cancer, or large varicose veins.

COMMENTARY

VTE occurring in association with air travel was first described as the "economy class syndrome" (1). Although highly publicized, the clinical importance of this association remains unclear. In the systematic review by Philbrick and colleagues, strengths and weaknesses of available studies addressing this issue are comprehensively evaluated and summarized.

In brief, overall risk for symptomatic VTE following air travel appears to be very low—approximately 27 VTEs per 1 million travelers. This is lower than commonly reported estimates of VTE in the general population (2). Philbrick and colleagues appropriately conclude that persons without risk factors for VTE do not warrant prophylaxis even with extended travel (> 8 h).

Perhaps a more clinically important question is whether persons with risk factors for VTE are at significantly increased risk for air-travel–related VTE. Unfortunately, such data on these persons are even more limited. Philbrick and colleagues identified 5 RCTs (all by the same investigative group) evaluating preventive measures in participants with risk factors for VTE (n = ~ 1700). In these studies, the risk for asymptomatic DVT detected by venous ultrasonography in participants who did not receive any preventive interventions was approximately 4.5%. However, as in other settings, the clinical significance of asymptomatic DVT is controversial. Interestingly, no episodes of symptomatic VTE occurred in either the intervention or control groups of these studies. As such, the need for DVT prophylaxis during air travel, even in persons with VTE risk factors, is far from established.

Given the very low incidence of symptomatic VTE overall, physicians may consider VTE prevention measures (compression stockings or low-dose low-molecular-weight heparin) only for persons at highest risk for VTE, such as those with prior VTE, cancer, or recent lower-extremity fracture. For these and other travelers, sensible recommendations to minimize risk for VTE include ensuring adequate hydration and leg exercises and ambulation to prevent venous stasis. Future studies evaluating air-travel–related VTE and its prevention should focus on these high-risk groups and use symptomatic VTE as the primary endpoint.

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Once-daily oral controller therapy with low-dose theophylline or montelukast was not effective in poorly controlled asthma

The American Lung Association Asthma Clinical Research Centers. **Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma.** Am J Respir Crit Care Med. 2007;175:235-42.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Allerg & Immunol ★★★★★☆☆ Pulmonology ★★★★★★☆

QUESTION

In patients with poorly controlled asthma while taking medication, what is the effectiveness of adding once-daily oral controller therapy to low-dose theophylline or montelukast?

METHODS

Design: Randomized placebo-controlled trial.
Allocation: {Concealed}†.*
Blinding: Blinded (clinicians, patients, {data collectors, outcome assessors, and data safety and monitoring committee}†).*
Follow-up period: 24 weeks.
Setting: 19 American Lung Association Asthma Clinical Research Centers (ALA-ACRC) in the United States.
Patients: 489 patients ≥ 15 years of age (mean age 40 y, 74% women, 61% white) who were diagnosed with asthma, were prescribed daily asthma medication for ≥ 1 year, had FEV_1 ≥ 50% of the predicted value, and had poor asthma control (score ≥ 1.5 on the Asthma Control Questionnaire [ACQ]). Patients continued their baseline medications. Exclusion criteria were use of oral corticosteroids, leukotriene antagonists, or theophylline within 4 weeks before randomization; ≥ 20 pack-years history of smoking; or significant illness.
Intervention: Theophylline, 300 mg/d (n = 161); montelukast, 10 mg/d (n = 164); or placebo (n = 164).
Outcomes: Annualized rate of episodes of poor asthma control (EPAC) (composite endpoint of > 30% drop in PEF for ≥ 2 consecutive d, increased use of rescue medication by > 4 metered-dose inhalations or 2 nebulizer treatments in 1 d, new use of oral corticosteroids, or unscheduled health care visit for asthma). Secondary outcomes were lung function (pre- and postbronchodilator [BD] FEV_1 and FVC), Asthma Symptom Utility Index (ASUI), Asthma Quality-of-Life Questionnaire (AQLQ), and ACQ scores; and adverse events. The study had 80% power to detect a 15% difference in the proportion of patients with ≥ 1 EPAC.
Patient follow-up: 90% (intention-to-treat analysis).

MAIN RESULTS

Overall, groups did not differ in the proportion of patients with ≥ 1 EPAC (Table); unadjusted annualized rates of EPAC; pre- or post-BD FVC; or mean change in ASUI, AQLQ, or ACQ scores. Theophylline led to greater improvements than placebo in pre-BD FEV_1 (P = 0.006 across all time points; 0.08 vs −0.01 L at 24 wks) and post-BD FEV_1 (P = 0.005 across all time points; 0.03 vs −0.02 L at 24 wks); montelukast led to greater improvements in pre-BD FEV_1 (P = 0.003 across all time points; 0.09 vs −0.01 L at 24 wks) but did not differ from placebo for post-BD FEV_1. At 4 weeks, there were more reports of nausea and nervousness with theophylline than with placebo or montelukast. Groups did not differ for any adverse event at 12 or 24 weeks.

CONCLUSION

Once-daily oral controller therapy with low-dose theophylline or montelukast was not effective in poorly controlled asthma.

Sources of funding: American Lung Association and Merck Company Foundation.

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*See Glossary.
†Information provided by author.

Theophylline or montelukast vs placebo in poorly controlled asthma at 4 to 24 weeks‡

Outcome	Theophylline	Montelukast	Placebo	RRI (95% CI)	NNH
≥ 1 EPAC§	53% (80/151)	–	52% (81/154)	0.73% (–19 to 25)	Not significant
				RRR (CI)	NNT
	–	49% (79/160)	52% (81/154)	6.1% (–17 to 25)	Not significant

‡EPAC = episode of poor asthma control; other abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from data in article.
§Composite endpoint of > 30% drop in PEF (theophylline vs montelukast vs placebo = 17% vs 16% vs 19%), use of rescue medication (42% vs 40% vs 38%), new use of oral corticosteroids (19% vs 14% vs 16%), or unscheduled health care visit for asthma (18% vs 16% vs 13%).

COMMENTARY

Inhaled corticosteroids (ICSs) are first-choice medications for initiating maintenance controller therapy in patients with mild persistent asthma (Step 2, Global INitiative for Asthma [GINA]) (1). Their effectiveness in improving asthma control and reducing exacerbations and asthma mortality are supported by clinical and epidemiologic studies over the past 3 decades. Adding long-acting β-agonists (LABAs) (Step 3, GINA) or leukotriene-receptor antagonists to ICSs improves clinical outcomes more than do ICSs alone (2).

The study by the ALA-ACRC compared the addition of oral montelukast, theophylline, or placebo to existing treatment regimens in patients with poorly controlled asthma. The results reinforce current guidelines showing little role for montelukast or theophylline in this setting. Most patients were white women, mean age of 40 years and asthma onset at mean age of 21 years. Of concern are the 18% of patients on LABA monotherapy without ICSs. Hence, generalizing these results to other populations should be done with caution.

Where does this leave montelukast and theophylline in overall asthma management? Montelukast is still first-line antiinflammatory controller therapy in children in whom oral or nonsteroidal medications are preferred. It is also effective for reducing rates of episodic viral-induced asthma exacerbations in preschool children (3) and managing exercise-induced asthma in cases where ICSs are ineffective (4).

In some countries, theophyllines are a low-cost alternative to ICSs. A subgroup analysis in the study by the ALA-ACRC showed improved asthma control, symptoms, and lung function in patients taking theophylline without ICSs. However, it is not clear whether the reduced cost of theophylline in this setting may be offset by other direct (emergency presentation, hospitalization) or indirect (school or work absenteeism) costs of asthma and longer-term asthma outcomes in comparison with ICS therapy.

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Review: Drugs for mild-to-moderate hypertension in pregnancy reduce risk for severe hypertension but not preeclampsia

Abalos E, Duley L, Steyn D, Henderson-Smart DJ. **Antihypertensive drug therapy for mild to moderate hypertension during pregnancy.** Cochrane Database Syst Rev. 2007;(1):CD002252.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Hospitalists ★★★★★★☆ Nephrology ★★★★★★☆

QUESTIONS

In pregnant women with mild-to-moderate hypertension, what are the benefits and risks of antihypertensive drugs? Is one type of antihypertensive drug better than another?

METHODS

Data sources: Cochrane Pregnancy and Childbirth Group's Trials Register (March 2006); Cochrane Central Register of Controlled Trials (2005, issue 3); and MEDLINE, LILACS, and EMBASE/Excerpta Medica (to November 2005).

Study selection and assessment: Randomized controlled trials (RCTs) that evaluated any antihypertensive drug (compared with placebo or no antihypertensive drug [control] or another type of antihypertensive drug) for mild-to-moderate hypertension (systolic blood pressure [BP] 140 to 169 mm Hg and diastolic BP 90 to 109 mm Hg) during pregnancy. Quasi-randomized studies and those involving treatment for < 7 days were excluded. 46 RCTs (n = 4282) met the selection criteria: 28 RCTs compared antihypertensive drugs with control (n = 3200) and 19 RCTs compared 2 types of antihypertensive drugs (n = 1282). Quality of individual trials was assessed based on allocation concealment, blinding, and withdrawals.

Outcomes: Severe hypertension, preeclampsia, fetal or neonatal death, preterm birth, and small-for-gestational age (SGA) infants.

MAIN RESULTS

Most trials were of moderate-to-poor quality. Meta-analysis showed that antihypertensive drugs reduced severe hypertension more than control, but groups did not differ for preeclampsia, fetal or neonatal death, preterm birth, or SGA infants (Table). In 9 RCTs (n = 904), β-blockers showed a borderline increase in SGA infants (relative risk 1.4, 95% CI 0.99 to 1.9) compared with control; however, in direct comparisons (5 RCTs, n = 478), β-blockers did not differ from methyldopa for this outcome. β-blockers reduced severe hypertension more than methyldopa (Table); calcium-channel blockers did not differ from β-blockers (1 RCT, n = 100) or methyldopa (2 RCTs, n = 46) for this outcome. Different types of antihypertensive drugs did not differ for preeclampsia, fetal or neonatal death, preterm birth, or SGA infants.

CONCLUSION

In pregnant women with mild-to-moderate hypertension, antihypertensive drugs reduce risk for severe hypertension more than placebo or no antihypertensive drug, but no other effects on maternal or perinatal outcomes were shown.

Sources of funding: Medical Research Council UK and World Health Organization.

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Antihypertensive (anti-HT) drugs vs placebo or no anti-HT drug (control) or another anti-HT drug for mild-to-moderate hypertension in pregnancy*

Outcomes	Number of trials (n)	Weighted event rates		RRR (95% CI)	NNT (CI)
		Anti-HT drugs	Control		
Severe hypertension	19 (2409)	9.7%	19%	50% (39 to 59)	10 (8 to 13)
Preeclampsia	22 (2702)	18%	18%	3% (–13 to 17)	Not significant
Fetal or neonatal death	26 (3081)	2.7%	3.7%	27% (–8 to 50)	Not significant
				RRI (CI)	NNH
Preterm birth	14 (1992)	28%	27%	2% (–11 to 16)	Not significant
Small-for-gestational age	19 (2437)	13%	12%	4% (–16 to 27)	Not significant
		β-blockers	Methyldopa	RRR (CI)	NNT (CI)
Severe hypertension	8 (493)	25%	32%	21% (1 to 37)	12 (6 to 275)

*Abbreviations defined in Glossary. Weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from relative risks and control event rates in article using a fixed-effects model.

COMMENTARY

The relative benefits and risks of antihypertensive therapy for mild-to-moderate hypertension in pregnancy remain unclear because maternal cardiovascular health and fetal well-being compete. Most hypertensive pregnant women are otherwise well and do not require blood pressure treatment over a period of months; the uteroplacental vasculature does not autoregulate blood flow, and so perfusion reflects maternal blood pressure.

Why treat mild-to-moderate hypertension in pregnancy? Although the stated objective is "to prevent or delay progression to preeclampsia," the excellent review by Abalos and colleagues provides no evidence that antihypertensive agents are likely to decrease the incidence of preeclampsia. This finding makes sense. Preeclampsia is not primarily a hypertensive disease, despite being defined by its most common clinical manifestations: hypertension and proteinuria. Rather, preeclampsia is a placental disorder that becomes apparent when fetal demands exceed uteroplacental supply. Trials and quantitative overviews should focus on the complications of preeclampsia, not on the diagnosis itself.

Abalos and colleagues reviewed a host of small, moderate-to-poor–quality trials. Antihypertensive drugs clearly decrease the risk for severe hypertension; whether this decrease alone is worthwhile is unclear because, although severe hypertension was common (30% with methyldopa use), no strokes were reported. Thus, the key issue becomes perinatal outcomes, which did not differ between groups, although confidence intervals were wide.

A definitive trial is needed. In the meantime, if a decision is made to give antihypertensive therapy, the clinician will need to make a choice among treatment options. Most guidance from the review relates to β-blockers; these subgroup analyses had the greatest power. β-blockers may be associated with lower birth weights. The conclusion that β-blockers may be more effective antihypertensive agents than methyldopa is tenuous (the data were heterogeneous, and the result was of borderline statistical significance). The scant neurodevelopmental data (even for methyldopa) are insufficient to guide choice of one antihypertensive agent over another. Antihypertensive choice is not informed by the many other subgroup analyses of few included trials. This large number of comparisons is acceptable for hypothesis generation in a retrospective and observational exercise, such as meta-analysis, but they do not provide clear evidence for clinical decisions.

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Stress echocardiography safely classified more patients as low risk for serious CAD than exercise electrocardiography

Jeetley P, Burden L, Stoykova B, Senior R. **Clinical and economic impact of stress echocardiography compared with exercise electrocardiography in patients with suspected acute coronary syndrome but negative troponin: a prospective randomized controlled study.** Eur Heart J. 2007;28:204-11.

Clinical impact ratings: Hospitalists ★★★★★☆ Cardiology ★★★★☆☆

QUESTION

In patients with suspected acute coronary syndrome and a negative cardiac troponin test, what are the clinical and economic effects of using stress echocardiography (SEcho) or exercise electrocardiography (ExECG) to predict risk for serious coronary artery disease (CAD)?

METHODS

Design: Randomized controlled trial.
Allocation: Unclear allocation concealment.*
Blinding: Unblinded.*
Follow-up period: Median 8.7 months.
Setting: Hospital in Harrow, Middlesex, England, United Kingdom.
Patients: 433 patients (mean age 61 y, 57% men) with suspected acute coronary syndrome, nondiagnostic ECG, negative cardiac troponin test result, and ≥ 2 risk factors for CAD. Patients with known CAD awaiting revascularization or contraindications for exercise were excluded.
Intervention: Risk for CAD was determined by SEcho using either treadmill or pharmacologic testing (n = 215) or ExECG (n = 218) (negative test = low risk, positive test = high risk, and inconclusive test = pretest risk as determined by the Thrombolysis in Myocardial Infarction [TIMI] risk score). The attending physician made management decisions based on the results of the stress tests. In general, patients at low risk were discharged, those at intermediate risk had further testing, and those at high risk were referred to a cardiologist.
Outcomes: Composite cardiac endpoint (cardiac death, myocardial infarction, or coronary artery revascularization), proportion of patients assigned to each risk stratum, use of additional diagnostic tests, and total cost of diagnosis.
Patient follow-up: 96% (intention-to-treat analysis).

MAIN RESULTS

Groups did not differ for the composite cardiac endpoint (Table). More patients were classified as low risk and fewer patients as intermediate or high risk after SEcho than after ExECG (Table). Fewer patients required further diagnostic testing (Table) and fewer additional tests were performed (44 vs 118) in the SEcho group. Although SEcho was more expensive than ExECG, after the additional tests were included the mean total cost of CAD diagnosis was lower in the SEcho group (Table).

CONCLUSIONS

In patients with suspected acute coronary syndrome and a negative cardiac troponin test, stress echocardiography had lower total costs than exercise electrocardiography by eliminating the need for additional diagnostic tests, without increasing overall risk for a cardiac event.

Sources of funding: Cardiac Research Fund and North West London Hospital Trust.

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*See Glossary.

Stress echocardiography (SEcho) vs exercise electrocardiography (ExECG) for initial investigation of patients with suspected acute coronary syndrome and negative troponin test†

Outcomes	SEcho	ExECG	RRR (95% CI)	NNT (CI)
Cardiac endpoint at median 8.7 mo	14%	15%	7% (–47 to 41)	Not significant
Additional diagnostic tests	20%	46%	57% (42 to 68)	4 (3 to 6)
			Absolute difference (CI)	*P* value
Low risk	77%	33%	44% (35 to 52)	< 0.0001
Intermediate risk	3%	39%	–36% (–43 to –29)	< 0.0001
High risk	20%	29%	–8% (–17 to –0.3)	0.04
Total cost of diagnosis (mean)	£367	£515	–£149	0.004

†Abbreviations defined in Glossary. RRR, NNT, absolute difference, and CI calculated from data in article.

COMMENTARY

What is the most appropriate initial stress test for patients with suspected low- to intermediate-risk unstable angina? Current guidelines recommend ExECG, citing the high cost of imaging (1). However, we need to account for all downstream costs and benefits of a test to determine the optimal testing strategy. The study by Jeetley and colleagues does just this for a cohort of patients with suspected acute coronary syndrome but a negative troponin test. Surprisingly, a strategy of initial SEcho was less expensive than starting with ExECG because more patients were classified as low risk with SEcho.

An unanswered question is the role of nuclear perfusion imaging. Given that the difference in total cost between SEcho and ExECG was 3 times the difference in cost between SEcho and the more expensive nuclear test, initial testing with stress nuclear testing could also be less expensive than ExECG if stress nuclear testing and SEcho have similar test characteristics, but that would depend on relative performance. Although meta-analyses have indicated that stress nuclear testing may yield more false-positive results than SEcho, both were estimated to lead to better outcomes than ExECG (2).

Another question is whether results from this single-site study in the United Kingdom apply to other settings. Although absolute costs will differ across countries, the relative costs of the different tests should be comparable. In addition, the intensity of care during the study (88% of patients with a positive stress test had angiography) was similar to care in the United States.

Confirmatory studies (in both acute and chronic angina) are needed before a clear recommendation can be made. However, SEcho is a reasonable and probably less expensive alternative to ExECG for patients with low- to intermediate-risk unstable angina.

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Review: Rescue percutaneous coronary intervention but not repeated fibrinolysis is effective for failed fibrinolysis in STEMI

Wijeysundera HC, Vijayaraghavan R, Nallamothu BK, et al. **Rescue angioplasty or repeat fibrinolysis after failed fibrinolytic therapy for ST-segment myocardial infarction: a meta-analysis of randomized trials.** J Am Coll Cardiol. 2007;49:422-30.

Clinical impact ratings: Hospitalists ★★★★★★☆ Cardiology ★★★★★☆☆

QUESTION

In patients with ST-segment elevation myocardial infarction (STEMI) in whom fibrinolytic therapy fails, what are the benefits and risks of rescue percutaneous coronary intervention (PCI) or repeated fibrinolytic therapy compared with conservative management?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica, Cochrane Library (to February 2006), and reference lists.

Study selection and assessment: Randomized controlled trials (RCTs) that compared a strategy of either rescue PCI or repeated fibrinolytic therapy with conservative management (no further immediate reperfusion therapy) in patients with STEMI in whom initial fibrinolytic therapy had failed (by angiographic or clinical definitions). 6 RCTs (n = 908, mean age range 57 to 63 y, 76% men) of rescue PCI and 3 RCTs (n = 410, mean age range 56 to 63 y, 75% men) of repeated fibrinolysis (with tissue-type plasminogen activator) met the selection criteria. Quality of individual trials was assessed using the Jadad scale.

Outcomes: All-cause mortality, heart failure, reinfarction, stroke, and major and minor bleeding.

MAIN RESULTS

Rescue PCI reduced risk for reinfarction more than conservative management, but reductions in mortality and heart failure did not reach statistical significance (Table). Rescue PCI increased risks for stroke and minor bleeding (Table). Groups did not differ for major bleeding (1 RCT, n = 285). Repeated fibrinolysis and conservative management did not differ for mortality, reinfarction, major bleeding (Table), heart failure (1 RCT, n = 283), or stroke (1 RCT, n = 283). Risk for minor bleeding was higher in the repeated fibrinolysis group (Table).

CONCLUSION

In patients with ST-segment elevation myocardial infarction in whom fibrinolytic therapy fails, rescue percutaneous coronary intervention reduces risk for reinfarction more than conservative management, but repeated fibrinolytic therapy does not provide any benefit.

Source of funding: No external funding.

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Rescue percutaneous coronary intervention (PCI) or repeated fibrinolytic therapy (FT) vs conservative management (control) for ST-segment elevation myocardial infarction with failed fibrinolysis*

Outcomes	Number of trials (n)	Weighted event rates		RRR/RRI (95% CI)	NNT/NNH (CI)
		Rescue PCI	Control		
Mortality	6 (908)	7.1%	10%	RRR: 31% (–5 to 54)	Not significant
Heart failure	4 (851)	13%	18%	RRR: 27% (0 to 46)	Not significant
Reinfarction	3 (700)	6.2%	11%	RRR: 42% (3 to 65)	NNT: 23 (15 to 312)
Composite endpoint†	3 (700)	30%	41%	RRR: 28% (12 to 41)	NNT: 9 (6 to 21)
Stroke	2 (592)	3.4%	0.7%	RRI: 398% (10 to 2148)	NNH: 38 (7 to 1475)
Minor bleeding	3 (620)	16%	3.6%	RRI: 358% (146 to 755)	NNH: 8 (4 to 20)
		Repeated FT	Control		
Mortality	3 (410)	11%	16%	RRR: 32% (–14 to 59)	Not significant
Reinfarction	2 (373)	12%	6.5%	RRI: 79% (–8 to 248)	Not significant
Major bleeding	2 (373)	4.1%	2.7%	RRI: 54% (–46 to 248)	Not significant
Minor bleeding	3 (410)	14%	7.8%	RRI: 84% (6 to 218)	NNH: 16 (6 to 213)

*Abbreviations defined in Glossary. RRR, RRI, NNT, NNH, and CI calculated from relative risks and control event rates in article using a fixed-effects model.
†Mortality, heart failure, or reinfarction.

COMMENTARY

It has been nearly impossible to conduct RCTs of rescue PCI in the United States because of the strong bias toward it. Guidelines considered rescue PCI to be a class 1 indication even before trials indicated its benefit (1). Although there are important differences among the trials included in the meta-analysis by Wijeysundera and colleagues, the data are sufficiently compelling to support routine performance of rescue PCI and its classification as a class 1 indication in STEMI guidelines. Rescue PCI increases bleeding complications, but a radial artery approach has been shown to reduce bleeding rates and may be particularly beneficial in this setting (2).

Many unanswered questions remain. In the 6 RCTs included in this meta-analysis, the time from administration of fibrinolytic therapy until it was deemed a failure varied from 60 minutes to several hours. If the interval was shorter, PCI might be even more beneficial. If it was too short, it might begin to resemble facilitated PCI, which seems to increase rather than decrease morbidity and mortality (3).

Administering a glycoprotein IIb/IIIa inhibitor shortly after a full dose of a fibrinolytic agent may be beneficial, but it clearly increases bleeding (4). The data are confounded because patients least likely to have major bleeding complications would preferentially be given such therapy, exaggerating any true benefit. True equipoise exists about whether to administer a IIb/IIIa inhibitor during rescue PCI; an RCT addressing this question is needed.

Should all patients treated with a fibrinolytic be transferred immediately to a center capable of performing PCI? Although Wijeysundera and colleagues did not address this issue directly, the data support such an approach. We are fully aware of the political and economic implications of this recommendation and that it will be greeted with antipathy in many quarters.

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Percutaneous coronary intervention plus optimal medical therapy was not more effective than medical therapy alone in stable CAD

Boden WE, O'Rourke RA, Teo KK, et al. **Optimal medical therapy with or without PCI for stable coronary disease.** N Engl J Med. 2007;356:1503-16.

Clinical impact ratings: GIM/FP/GP ★★★★★★★ Hospitalists ★★★★★★☆ Cardiology ★★★★★★☆

QUESTION

In patients with stable coronary artery disease (CAD), is percutaneous coronary intervention (PCI) plus optimal medical therapy (OMT) more effective than OMT alone for preventing cardiovascular events?

METHODS

Design: Randomized controlled trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE] trial).

Allocation: Unclear allocation concealment.*

Blinding: Blinded (outcome adjudication committee).*

Follow-up period: Median 4.6 years (range 2.5 to 7.0 y).

Setting: 50 centers in the United States and Canada.

Patients: 2287 patients (mean age 62 y, 85% men) with stable CAD (stenosis ≥ 70% in ≥ 1 proximal epicardial coronary artery and objective evidence of myocardial ischemia, or ≥ 1 coronary stenosis ≥ 80% and classic angina without provocative testing). Exclusion criteria included persistent class IV angina, a markedly positive stress test, refractory heart failure or cardiogenic shock, ejection fraction < 30%, revascularization in ≤ 6 months, and coronary anatomy not suitable for PCI.

Intervention: PCI (with bare-metal stents in most patients) plus OMT (antiischemic therapy, aggressive therapy to optimize lipid levels, and a lifestyle intervention) (n = 1149) or OMT alone (n = 1138).

Outcomes: Composite endpoint of death or nonfatal myocardial infarction (MI). Secondary outcomes were a composite endpoint of death, MI, or stroke; hospitalization for unstable angina with negative biomarkers; and additional revascularization procedures.

Patient follow-up: 91% (intention-to-treat analysis).

MAIN RESULTS

Groups did not differ for the composite endpoint of death or MI; the composite endpoint of death, MI, or stroke; or hospitalization for unstable angina (Table). Risk for additional revascularization procedures was lower in the PCI plus OMT group (Table).

CONCLUSION

In patients with stable coronary artery disease, initial management with percutaneous coronary intervention plus optimal medical therapy was not more effective than optimal medical therapy alone for preventing cardiovascular events.

Sources of funding: U.S. Department of Veterans Affairs; Canadian Institutes of Health Research; Merck; Pfizer; Bristol-Myers Squibb; Fujisawa; Kos Pharmaceuticals; Datascope; Astra-Zeneca; Key Pharmaceutical; Sanofi-Aventis; First Horizon; GE Healthcare.

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*See Glossary.

Percutaneous coronary intervention (PCI) plus optimal medical therapy (OMT) vs OMT alone in stable coronary artery disease at median 4.6 years†

Outcomes	PCI plus OMT	OMT alone	RRI (95% CI)	NNH
Death or MI	19.0%	18.5%	4.5% (–12 to 24)	Not significant
Death, MI, or stroke	20.0%	19.5%	4.5% (–12 to 23)	Not significant
Hospitalization for ACS	12.4%	11.8%	6.5% (–15 to 34)	Not significant
			RRR (CI)	NNT (CI)
Additional revascularization	21%	33%	35% (25 to 44)	9 (7 to 13)

†MI = myocardial infarction; ACS = acute coronary syndrome; other abbreviations defined in Glossary. RRI, RRR, NNH, NNT, and CI calculated from hazard ratios in article.

COMMENTARY

Most MIs occur from minimally occlusive CAD (1). Thus, it is not surprising that PCI of high-grade CAD is more effective than medical therapy in relieving angina pectoris but not in reducing MI or death in patients with chronic stable CAD (2). However, many clinicians refer patients with stable CAD to PCI without attempting OMT, for fear of litigation should the patient have an MI without PCI. The results of the COURAGE trial by Boden and colleagues suggest that these fears are unfounded. Although approximately 30% of patients randomized to OMT had subsequent PCI, the incidence of death or MI did not differ between groups. Early in the trial, a small decrease in prevalence of angina was shown in patients randomized to PCI; however, by 5 years results for the 2 groups were similar.

Some critics have pointed out that the use of drug-eluting stents in COURAGE was suboptimal; however, no evidence exists that drug-eluting stents decrease the incidence of death or MI compared with bare-metal stents. Others say that the results are less applicable to non–Veterans Administration centers. Yet others object to the decision for randomization being made after a diagnostic coronary angiogram was done—once the angiogram reveals a stenosis suitable for PCI according to guidelines, they claim that the risk associated with PCI is small, and the patient will benefit from immediate relief of angina. However, if one follows current guidelines for evaluation of patients with stable CAD (3) and excludes those with severe left ventricular dysfunction, evidence of left main CAD, or the acute coronary syndrome, most patients should be safely controlled on OMT, as defined in COURAGE. Such patients need to be referred for angiography only if they show evidence of progressive angina or myocardial ischemia. Even in patients with the acute coronary syndrome, the ICTUS trial recently suggested that a strategy of selective, symptom-determined angiography and revascularization may be as good as routine revascularization (4).

Only time will tell whether we can put the interests of our patients above our own economic interests and have the courage to implement OMT, as defined in COURAGE, with its resultant cost savings. If we fail this challenge, we risk having the decision imposed upon us, which would probably not benefit our patients or ourselves.

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Review: Drug-eluting stents are more effective than bare-metal stents for reducing acute MI at 6 to 12 months after implantation

Moreno R, Fernandez C, Calvo L, et al. **Meta-analysis comparing the effect of drug-eluting versus bare metal stents on risk of acute myocardial infarction during follow-up.** Am J Cardiol. 2007;99:621-5.

Clinical impact ratings: Cardiology ★★★★★☆☆

QUESTION

In patients undergoing stent implantation, are drug-eluting stents (DESs) more effective than bare-metal stents (BMSs) for reducing risk for acute myocardial infarction (MI)?

METHODS

Data sources: MEDLINE and lists of conference abstracts from the European Society of Cardiology, American College of Cardiology, American Heart Association, and Transcatheter Cardiovascular Therapeutics (to January 2006).

Study selection and assessment: Randomized controlled trials (RCTs) that compared DESs with BMSs. 25 RCTs (n = 9791, mean age range 59 to 67 y) met the selection criteria. The DESs evaluated contained sirolimus (11 RCTs), paclitaxel (7 RCTs), tacrolimus (2 RCTs), zotarolimus (1 RCT), everolimus (3 RCTs), and biolimus (1 RCT).

Outcomes: Acute MI (new increase in serum creatine kinase level ≥ 2 times the upper limit of normal reference range, concomitant increase in MB fraction of enzyme, and periprocedural infarction), Q-wave MI, and non–Q-wave MI.

MAIN RESULT

Meta-analysis showed that DESs reduced risk for acute MI more than did BMSs (Table). DESs and BMSs did not differ for Q-wave or non–Q-wave MI (Table).

CONCLUSION

Drug-eluting stents are more effective than bare-metal stents for reducing risk for acute myocardial infarction at 6 to 12 months after implantation.

Source of funding: Not stated.

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Drug-eluting stents vs bare-metal stents at 6 to 12 months after implantation*

Outcomes	Number of trials (n)	Weighted event rates	RRR (95% CI)	NNT (CI)
Acute MI	25 (9703)	3.3% vs 4.2%	20% (2.9 to 35)	118 (69 to 829)
Non–Q-wave MI	19 (6452)	2.7% vs 3.4%	20% (–5.8 to 39)	Not significant
			RRI (CI)	NNH
Q-wave MI	19 (6452)	0.71% vs 0.59%	20% (–34 to 118)	Not significant

*MI = myocardial infarction; other abbreviations defined in Glossary. Weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from odds ratios and control event rates in article using a fixed-effects model.

COMMENTARY

Intracoronary stents are widely regarded as a major therapeutic advance in cardiology because they reduce the rate of angiographic restenosis and subsequent need for repeated percutaneous coronary intervention (PCI). However, compared with balloon angioplasty (BA) and restricted stenting, routine coronary stenting is not associated with reductions in mortality, MI, or coronary artery bypass surgery (1). The higher upfront cost of stenting is outweighed by the benefit of reducing risk for restenosis and associated costs of repeated PCI. However, it is not clear if a similar magnitude of benefit is seen in the "real world," where routine angiographic assessment of restenosis is not performed.

In theory, DESs should have taken this benefit to higher levels as the mechanical scaffolding effect was coupled with drugs to reduce risk for restenosis. Indeed, in the meta-analysis by Kastrati and colleagues, risk for restenosis was further reduced but risk for MI or death was not reduced with DESs compared with BMSs during long-term follow up. The lack of benefit is not unexpected given that "hard" clinical endpoints did not differ between BMSs and BA; however, while the study reduces overall concerns of increased events with DESs, the increase in late stent thrombosis and the apparent lack of benefit in patients with diabetes remain issues of concern.

The meta-analysis by Moreno and colleagues suggested reduced risk for MI using a very conservative creatine-kinase–based definition. Lesser degrees of myocardial necrosis, which may be prognostically important, would have been missed. It is also not clear from the data whether there is a temporal association between avoidance of MI and restenosis. Finally, Moreno and colleagues selectively looked at MI in isolation, whereas patients are likely to be more interested in survival free of MI, as reported by Kastrati and colleagues (2). In addition, the recently published results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial may call into question the overall value of PCI (predominantly BMSs) in stable populations with CAD (3).

DESs have a role in the management of patients with stable CAD, but this role should not be overemphasized. The recent increase in the United States and Canada of DES utilization rates from 75% to 90% is not justified based on present RCT evidence.

A more rational use of DESs involves the incorporation of clinical and angiographic data to select patients at high risk for restenosis or, if restenosis develops, those at high risk for having more severe consequences. Clinical criteria would include the presence of diabetes or renal insufficiency or a history of bypass surgery. Angiographic criteria include small-vessel diameter and longer lesions, unprotected left main lesions, or disease of the ostial or proximal left anterior descending artery.

(continued on page 14)

Review: Sirolimus-eluting stents do not differ from bare-metal stents for long-term survival in CAD

Kastrati A, Mehilli J, Pache J, et al. **Analysis of 14 trials comparing sirolimus-eluting stents with bare-metal stents.** N Engl J Med. 2007;356:1030-9.

Clinical impact ratings: Cardiology ★★★★★☆☆

QUESTION

In patients with coronary artery disease (CAD), how do sirolimus-eluting stents (SESs) compare with bare-metal stents (BMSs) for long-term survival?

METHODS

Data sources: MEDLINE; National Institutes of Health clinical trials registry; Cochrane Central Register of controlled trials; lists of conference abstracts from American College of Cardiology, American Heart Association, and European Society of Cardiology; and hand searches of clinical trials in cardiology and relevant studies from major medical journals (January 2002 to September 2006).

Study selection and assessment: Randomized controlled trials (RCTs) that compared SESs with BMSs in patients with CAD and had mean follow up ≥ 1 year. 14 RCTs (n = 4958, mean age range 59 to 67 y, mean follow-up range 12 to 59 mo) met the selection criteria. Quality assessment of individual studies was based on allocation concealment, blinded outcome assessment, and intention-to-treat analysis.

Outcomes: All-cause death. Secondary outcomes were stent thrombosis and the composite outcomes of death or myocardial infarction (MI); and death, MI, or reintervention (major adverse cardiac events).

MAIN RESULTS

Meta-analysis showed that groups did not differ for all-cause death, stent thrombosis (overall), or the composite endpoint of death or MI (Table). SESs led to a lower incidence of the composite endpoint of death, MI, or reintervention than did BMSs (Table). After 1 year, SESs increased risk for stent thrombosis more than did BMSs (0.6% vs 0.05%, P = 0.02).

CONCLUSION

Sirolimus-eluting stents do not differ from bare-metal stents for long-term survival in patients with coronary artery disease.

Source of funding: No external funding.

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Sirolimus-eluting stents vs bare-metal stents in coronary artery disease at 12 to 59 months*

Outcomes	Number of trials (n)	Weighted event rates	RRI (95% CI)	NNH
All-cause death	14 (4958)	6.1% vs 6.0%	2.9% (–20 to 29)	Not significant
Stent thrombosis (overall)		0.3% vs 0.3%	9.0% (–36 to 86)	Not significant
			RRR (CI)	NNT (CI)
Death or MI		9.9% vs 10%	2.8% (–15 to 18)	Not significant
Death, MI, or reintervention†		12% vs 26%	53% (42 to 63)	8 (7 to 10)

*MI = myocardial infarction; other abbreviations defined in Glossary. Weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from hazard ratios and control event rates in article using a random-effects model.
†Reintervention = major adverse cardiac events.

COMMENTARY *(continued from page 13)*

Repeated revascularization is not entirely a result of clinical or angiographic within-stent restenosis, particularly after the first year. While the stented segment may remain stable, disease progression in other segments is 4 times more likely to be responsible for adverse clinical outcomes than is stent restenosis (4). As such, aggressive risk factor modification and vascular protection are mandatory.

Finally, all new advances seem to come at a cost: The cost for DESs is a higher risk for late stent thrombosis. However, although the evidence base shows that risk exists, the magnitude is small—around 4 to 6 per 1000 patients stented. While the risk could possibly be mitigated by concomitant and prolonged use of aspirin and clopidogrel, the combination is probably associated with increased risk for bleeding; the magnitude of serious bleeding may be similar to the stent thromboses avoided. Unfortunately, data outlining the optimal duration of dual therapy are not forthcoming. At least 1 year of dual antiplatelet therapy is required for all DES implants. Therapy extending beyond 1 year may be indicated for patients at high risk for late stent thrombosis or severe consequences from thrombosis—for example, unprotected left main-stem stenosis or multiple stents.

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Review: Evidence from observational studies, but not randomized trials, suggests that long-term aspirin prevents colorectal cancer

Dubé C, Rostom A, Lewin G, et al. **The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force.** Ann Intern Med. 2007;146:365-75.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Gastroenterology ★★★★★★☆ Oncology ★★★★★☆☆

QUESTION

Is aspirin effective and safe for primary prevention of colorectal cancer?

METHODS

Data sources: MEDLINE (to December 2006), preMEDLINE (to April 2005), EMBASE/Excerpta Medica (to April 2005), the Cochrane Library (Issue 4, 2004), and the PubMed Cancer subset.

Study selection and assessment: English-language studies that evaluated the efficacy of aspirin for primary prevention of colorectal cancer in persons at "average" risk and systematic reviews that assessed the harms of long-term aspirin use. Studies of familial colon cancer were excluded. 4 randomized controlled trials (RCTs) (n = 63 340), 9 cohort studies (n = 1 303 573), 13 case–control studies (n = 1 148 086), and 12 reviews met the selection criteria.

Outcomes: Colorectal cancer mortality, colorectal cancer, colorectal adenoma, hemorrhagic stroke, and gastrointestinal bleeding.

MAIN RESULTS

Evidence from cohort and case–control studies, but not RCTs, indicated that long-term aspirin use prevented colorectal cancer mortality, colorectal cancer, and colorectal adenomas (Table). Aspirin was effective for secondary prevention of colorectal adenomas (Table). The benefits of aspirin were greater with higher doses and longer duration of treatment. Aspirin increased risks for hemorrhagic stroke and gastrointestinal bleeding (Table), especially at higher doses.

CONCLUSIONS

Evidence from observational studies suggests that aspirin prevents colorectal adenomas, colorectal cancer, and death from colorectal cancer, but these findings were not confirmed by 2 randomized trials. Aspirin is associated with increased risks for hemorrhagic stroke and gastrointestinal bleeding.

Sources of funding: Centers for Disease Control and Prevention for the Agency for Healthcare Research and Quality and the U.S. Preventive Services Task Force.

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Aspirin for prevention of colorectal cancer in persons at average risk*

Outcomes	Study design	Number of studies (n)	Summary RRR/RRI [95% CI]†
Colorectal cancer mortality	RCT	1 (39 876)	Not significant
	Cohort	1 (1 083 531)	RRR: 28% to 42%‡
Colorectal cancer	RCT	2 (61 947)	RRI: 2% (–16 to 25)
	Cohort	5 (203 294)	RRR: 22% (3 to 37)
	Case–control	7 (23 797)	RRR: 10% to 68%‡
Colorectal adenoma	RCT	1 (22 071)	RRR: 14% (–10 to 32)
	Cohort	2 (137 346)	RRR: 28% (15 to 39)
	Case–control	5 (1 126 059)	RRR: 13% (2 to 23)
Colorectal adenoma (secondary prevention)	RCT	2 (1393)	RRR: 18% (5 to 30)
	Cohort	2 (2769)	RRR: 18% to 48%‡
	Case–control	2 (934)	RRR: 9% to 91%‡
Hemorrhagic stroke	RCT	1 SR	RRI: 84% (24 to 174)
Gastrointestinal bleeding	RCT, cohort, case–control	7 SRs	RRI: 60% to 210%‡

*RCT = randomized controlled trial; COX = cyclooxygenase; SR = systematic review; other abbreviations defined in Glossary.

†RRR, RRI, and CI calculated from relative risk and CI in article using a random-effects model.

‡Range of RRRs or RRIs in individual studies or subgroups; no summary relative risk provided because of heterogeneity among studies.

COMMENTARY

The comprehensive review by Dubé and colleagues highlights notable discrepancies between RCTs and observational studies regarding aspirin's efficacy as a chemopreventive agent. Although the observational studies showed preventive effects for first adenoma incidence, colorectal cancer incidence, and colorectal cancer mortality among regular aspirin users, the 2 RCTs measuring these endpoints were negative.

We usually regard RCTs as the gold standard, trumping the findings of observational studies because the latter are subject to bias through confounding factors. Although a good-quality observational study can adjust for such known confounders as smoking status, body mass index, and physical activity, unknown factors may affect both exposure and risk for outcome (1). Despite our usual reliance on RCTs to provide definitive answers to clinical questions, in this instance the weight of evidence from multiple observational studies points to a true chemopreventive effect. While the RCTs were well-designed, each answered only a narrow question and did not negate the findings of the many observational studies that showed consistent, biologically plausible results.

The Physicians Health Study, the first RCT evaluating aspirin as a chemopreventive agent, found no reduction in colorectal cancer incidence among persons randomized to aspirin, but the dose was relatively low (325 mg every other day), and follow-up was only 5 years (2). Because the progression to adenoma and carcinoma typically proceeds over the course of a decade, one might see a divergence between aspirin and placebo in studies with longer follow-up. The Women's Health Study (3) provided exposure and follow-up of 10 years but used an even lower dose of aspirin (100 mg every other day). Thus, the negative findings of these RCTs may have been a result of inadequate dose or duration.

The trials of aspirin for adenoma prevention provide additional evidence that insufficient exposure and length of follow-up are important factors to consider in the RCTs with negative results. Although the 2 RCTs cited above found no reduction in the incidence of a first colorectal adenoma, a subsequent RCT of participants with a previous adenoma found an absolute risk reduction of 9% in patients who took aspirin, 81 mg, for at least 1 year (4). Because this trial recruited patients who were already predisposed to polyp formation, it was sufficiently powered. In addition, it involved a mandatory follow-up colonoscopy (not included in the earlier RCTs).

In the review by Rostom and colleagues, the RCT evidence for chemopreventive effects of nonaspirin NSAIDs was limited to recent trials of COX-2 inhibitors because other agents have been evaluated only in observational studies. The RCT data for COX-2 inhibitors and the observational data for other NSAIDs are consistent and convincing for reductions in recurrent adenomas (with COX-2 inhibitors and other nonaspirin NSAIDs) and colorectal cancer (with nonselective,

(continued on page 16)

Review: NSAIDs and COX-2 inhibitors may prevent colorectal cancer but increase gastrointestinal and cardiovascular harm

Rostom A, Dubé C, Lewin G, et al. **Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force.** Ann Intern Med. 2007;146:376-89.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Gastroenterology ★★★★★★☆ Oncology ★★★★☆☆☆

QUESTION

Are nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors effective and safe for primary prevention of colorectal cancer?

METHODS

Data sources: MEDLINE (to December 2006), preMEDLINE (to April 2005), EMBASE/Excerpta Medica (to April 2005), the Cochrane Library (Issue 4, 2004), the PubMed Cancer subset, U.S. Food and Drug Administration News Digest, and Health Canada's Health Product Information mailing list.

Study selection and assessment: English-language studies that evaluated the efficacy of NSAIDs or COX-2 inhibitors for primary prevention of colorectal cancer in persons at "average" risk and systematic reviews that assessed the harms of these agents. Studies of familial colon cancer were excluded. 4 randomized controlled trials (RCTs) (n = 6056), 5 cohort studies (n = 486 264), 19 case–control studies (n = 69 788), and 23 reviews met the selection criteria.

Outcomes: Colorectal cancer mortality, colorectal cancer, colorectal adenoma, cardiovascular events, and gastrointestinal harm.

MAIN RESULTS

Evidence from cohort and case–control studies showed that long-term NSAID use prevented colorectal cancer and colorectal adenoma (Table). COX-2 inhibitors were effective for secondary prevention of colorectal adenomas (Table). The benefits of NSAIDs were greater with higher doses and longer duration of treatment in some, but not all, studies. Nonnaproxen nonaspirin NSAIDs and COX-2 inhibitors increased risk for serious cardiovascular events (Table). Nonaspirin NSAIDs increased risk for peptic ulcers and gastrointestinal bleeding, but COX-2 inhibitors did not (Table).

CONCLUSIONS

Evidence from observational studies suggests that nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) inhibitors prevent colorectal adenomas and colorectal cancer. COX-2 inhibitors prevent recurrence of colorectal adenomas. Both NSAIDs and COX-2 inhibitors increase risk for cardiovascular harm.

Sources of funding: Centers for Disease Control and Prevention for the Agency for Healthcare Research and Quality and the U.S. Preventive Services Task Force.

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Nonsteroidal antiinflammatory drugs (NSAIDs) for prevention of colorectal cancer in persons at average risk*

Outcomes	Study design	Type of NSAID	Number of studies (n)	Summary RRR/RRI (95% CI)†
Colorectal cancer mortality	Cohort	Ibuprofen	1 (113 538)	RRR: 7% (–30 to 40) (bowel) RRI: 46% (–10 to 130) (rectal)
Colorectal cancer	Cohort	Nonaspirin	3 (370 821)	RRR: 21% to 40%‡
	Case–control	Nonaspirin	4 (18 324)	RRR: 30% (22 to 37)
		Any	5 (16 735)	RRR: 43% (32 to 53)
Colorectal adenoma	Case–control	Nonaspirin	4 (14 071)	RRR: 45% (24 to 60)
		Any	5 (3951)	RRR: 43% (29 to 54)
Colorectal adenoma (secondary prevention)	RCT	COX-2 inhibitor	3 (5972)	RRR: 28% (23 to 32)
	Cohort	Any	1 (1905)	RRR: 36% (15 to 52)
Serious cardiovascular events	RCT	Ibuprofen	1 SR	RRI: 51% (–4 to 137)
	RCT	Diclofenac	1 SR	RRI: 63% (12 to 137)
	RCT	COX-2 inhibitor	2 SRs	RRI: 42% (13 to 78), 89% (3 to 245)
Gastrointestinal harm	RCT, cohort, case–control	Nonaspirin	1 SR	RRI: 170% to 436%‡
	RCT	COX-2 inhibitor	6 SRs	Not different from placebo

*RCT = randomized controlled trial; COX = cyclooxygenase; SR = systematic review; other abbreviations defined in Glossary.
†RRR, RRI, and CI calculated from relative risks and CI in article using a random-effects model.
‡Range of RRRs or RRIs in individual studies; no summary relative risk provided because of heterogeneity among studies.

COMMENTARY *(continued from page 15)*

nonaspirin NSAIDs). Buttressing the observational data is the further risk reduction observed with increased treatment dose and duration. Although these findings may be subject to bias because of confounding by indication, sufficient biological plausibility exists to suggest a real, if modest, chemopreventive effect.

For a drug to be a useful chemopreventive agent, it must have substantial efficacy with low toxicity because it would be used over the long term in healthy individuals. The authors of the 2 reviews pointed out that significant long-term risks are associated with each agent. The gastrointestinal toxicity associated with all agents (albeit at a lower rate among the COX-2 inhibitors) and the cardiovascular morbidity associated with COX-2 inhibitors and many nonaspirin NSAIDs preclude their use for the primary indication of chemoprevention.

More important, the chemopreventive potential of these drugs is marginalized by the currently recommended and proven strategy of screening for colorectal cancer. Because screening with colonoscopy or other methods decreases risk for colon cancer by 30% to 70%, the additional benefits from a chemopreventive agent do not outweigh the potential toxic effects.

Individuals prescribed aspirin or other NSAIDs for other conditions (e.g., cardiovascular protection or arthritis) may also derive a modest chemopreventive effect; however, this does not preclude the need for screening. The toxicities associated with these drugs do not justify their primary use for chemoprevention in persons at average risk for colon cancer.

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Review: Anticoagulants increase intracerebral bleeding and do not reduce death or disability in acute cardioembolic stroke

Paciaroni M, Agnelli G, Micheli S, Caso V. **Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials.** Stroke. 2007;38:423-30.

Clinical impact ratings: Referred Care ★★★★★★☆ Emerg Med ★★★★★★☆ Cardiology ★★★★★☆☆ Hematology ★★★★★★☆ Neurology ★★★★★★☆

QUESTION

In patients with acute cardioembolic stroke, are anticoagulants effective and safe as initial treatment?

METHODS

Data sources: MEDLINE and EMBASE/Excerpta Medica (1980 to February 2006), the Cochrane Library (2006, issue 1), bibliographies of relevant studies, and abstracts of major international meetings.

Study selection and assessment: Randomized controlled trials (RCTs) that compared anticoagulants (unfractionated heparin, low-molecular-weight heparin, or heparinoids) with other treatments or placebo in patients (randomized within 48 h of stroke onset) who received an objective diagnosis of stroke of presumed cardioembolic origin and were assessed using objective methods. 7 RCTs (n = 4624) were included. 3797 patients had atrial fibrillation, and 827 had other mixed cardioembolic sources. The anticoagulants were intravenous dalteparin (1 RCT), intravenous heparin (2 RCTs), subcutaneous heparin (1 RCT), intravenous danaparoid (1 RCT), subcutaneous nadroparin (1 RCT), and tinzaparin (1 RCT). Studies were assessed for allocation methods, allocation concealment, blinding, and completeness of follow-up.

Outcomes: A composite outcome of death or disability at ≥ 3 months, all strokes or early recurrent stroke within 14 d, and symptomatic intracranial bleeding.

MAIN RESULTS

Anticoagulants did not differ significantly from placebo or aspirin for death or disability, all strokes, or recurrent stroke, but they increased the risk for symptomatic intracranial bleeding (Table).

CONCLUSIONS

In patients with acute cardioembolic stroke, anticoagulants do not differ significantly from placebo or aspirin for the composite outcome of death or disability or for stroke, including recurrent early stroke. However, they increase the risk for intracranial bleeding.

Source of funding: No external funding.

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Anticoagulants vs aspirin or placebo for acute cardioembolic stroke*

Outcomes	Number of RCTs (n)	Weighted event rates		RRI (95% CI)	NNH (CI)
		Anticoagulants	Aspirin or placebo		
Death or disability at ≥ 3 mo	6 (4568)	73.8%	73.5%	0 (–5.4 to 5.3)	Not significant
All strokes	4 (4031)	4.3%	3.7%	17% (–25 to 82)	Not significant
Intracranial bleeding	(5)†	2.5%	0.7%	185% (19 to 572)	78 (25 to 759)
				RRR (CI)	NNT
Recurrent stroke at 14 d	(5)†	3.0%	4.9%	31% (–5.7 to 55)	Not significant

*RCT = randomized controlled trial; other abbreviations defined in Glossary. RRR, RRI, NNH, and CI calculated from odds ratio in article using a random-effects model.

†Information provided by author.

COMMENTARY

Ischemic stroke was commonly treated with short-term anticoagulation 10 years ago, most frequently with heparin. A series of randomized trials, many included in this meta-analysis by Paciaroni and colleagues, showed that there was no benefit to anticoagulation when given within hours of an ischemic stroke and that it increased the risk for major hemorrhagic complications. However, cardioembolic strokes were not well-represented in most of these trials.

The benefit of long-term anticoagulation with warfarin in patients with cardioembolic stroke is well-established. Some experts have argued that short-term anticoagulation in patients with recent cardioembolic stroke should reduce the risk for early recurrence and that this benefit is likely to outweigh the risk for hemorrhagic complications. This meta-analysis argues that they are wrong, and in doing so, it eliminates one of the last widely accepted indications for full-dose heparin after ischemic stroke.

This meta-analysis extracted data from subgroups in larger trials (including data not previously reported) and thus adds to the literature rather than just summarizing it. With the data clearly presented, the conclusions are obvious: Any benefit from short-term anticoagulation in reducing risk for recurrent ischemic stroke is outweighed by the risk for hemorrhagic stroke, with no net benefit in mortality and disability.

Prophylaxis of deep venous thrombosis remains an uncertain indication for heparins in nonambulatory patients with stroke and is currently being studied in randomized trials. The lower doses required for prophylaxis are more effective than compression devices, but this benefit may be balanced by a greater risk for brain hemorrhage (1). Patients with cardioembolic transient ischemic attack may also benefit from short-term anticoagulation since the risk for recurrence is particularly high in these patients, and the risk for brain hemorrhage should be substantially lower in the absence of major brain infarction. However, this indication needs to be evaluated in trials (2). Short-term aspirin does improve outcomes after ischemic stroke and should be given to all patients.

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Early infusion of high-dose omeprazole before endoscopy reduced the need for endoscopic therapy

Lau JY, Leung WK, Wu JC, et al. **Omeprazole before endoscopy in patients with gastrointestinal bleeding.** N Engl J Med. 2007; 56:1631-40.

Clinical impact ratings: Gastroenterology ★★★★★★☆

QUESTION

In patients with bleeding peptic ulcers, does early intravenous (IV) infusion of high-dose omeprazole before endoscopy reduce the need for endoscopic therapy?

METHODS

Design: Randomized placebo-controlled trial.

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, {data collectors, outcome assessors, data analysts, and data safety and monitoring committee}†).*

Follow-up period: Up to 30 days from randomization.

Setting: Accident and Emergency Department (ED) at the Prince of Wales Hospital, Hong Kong, China.

Patients: 638 patients ≥ 18 years of age who presented to the ED with upper gastrointestinal bleeding (melena or hematemesis with or without hypotension). Exclusion criteria included continued hypotensive shock despite resuscitation, allergy to proton pump inhibitors (PPIs), regular use of aspirin for cardiovascular protection, or pregnancy.

Intervention: Omeprazole (IV bolus injection, 80 mg followed by continuous infusion, 8 mg/h until endoscopic examination the next morning) (n = 319), or matching placebo (n = 319).

Outcomes: Need for endoscopic therapy. Secondary outcomes were actively bleeding ulcers (spurting or oozing), all-cause mortality at 30 days, recurrent bleeding at 30 days, length of hospital stay, urgent endoscopy, emergency surgery, or blood transfusion.

Patient follow-up: 631 patients (mean age 62 y, 65% men) (99% included in the intention-to-treat analysis).

MAIN RESULTS

Fewer patients in the omeprazole group had endoscopic therapy and actively bleeding ulcers than did the placebo group (Table). The omeprazole group had more patients who stayed in hospital for < 3 days than did the placebo group (Table). Groups did not differ for all-cause mortality, recurrent bleeding, urgent endoscopy, blood transfusion, or emergency surgery.

CONCLUSION

Early intravenous infusion of high-dose omeprazole before endoscopy reduced the need for endoscopic therapy and actively bleeding peptic ulcers.

Source of funding: Institute of Digestive Disease, Chinese University of Hong Kong.

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*See Glossary.

†Information provided by author.

Early intravenous infusion of high-dose omeprazole vs placebo before endoscopy in patients with bleeding peptic ulcers at first endoscopic examination‡

Outcomes	Omeprazole	Placebo	RRR (95% CI)	NNT (CI)
Endoscopic therapy	19%	28%	33% (10 to 49)	11 (8 to 36)
Actively bleeding ulcers	6.4%	15%	56% (17 to 77)	13 (9 to 40)
			RBI (CI)	
Hospital stay < 3 days	61%	49%	23% (7.0 to 42)	9 (5 to 30)

‡Abbreviations defined in Glossary. RRR, RBI, NNT, and CI calculated from control event rates and relative risks in article.

COMMENTARY

Although treatment with PPIs is often initiated for upper gastrointestinal bleeding (UGIB) before endoscopy establishes its cause, PPIs have previously been shown only to improve clinical outcomes among patients with bleeding ulcers (1). The study by Lau and colleagues showed that preendoscopic administration of high-dose IV PPI therapy reduced the proportion of patients with active bleeding at endoscopy, reduced the requirement for endoscopic therapy for ulcer bleeding, and shortened hospital stay. Although the study used IV omeprazole, which is not available in North America, any benefit from PPI therapy is likely to be a class effect. These results, however, may not necessarily be replicated in North America where a lower proportion of UGIB originates from ulcer disease than in Hong Kong. Furthermore, PPI therapy for ulcer bleeding has been shown to be more effective in studies performed in Asia than in those done elsewhere (1, 2).

Since initiation of IV PPI therapy for UGIB on first presentation carries minimal or no risk, it may be a reasonable strategy, although potentially expensive. Physicians should use the IV PPI that is available to them and give at least the same high dose used in this study (80 mg bolus and 8 mg/h infusion). However, this is not a panacea and does not replace the need for adequate resuscitation, careful monitoring, and appropriate endoscopic management. PPI treatment should be discontinued for patients found at endoscopy not to have bled from an ulcer.

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Review: Neoadjuvant chemoradiotherapy and chemotherapy improve survival in operable esophageal cancer

Gebski V, Burmeister B, Smithers BM, et al. **Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis.** Lancet Oncol. 2007;8:226-34.

Clinical impact ratings: Gastroenterology ★★★★★☆☆ Oncology ★★★★★★★

QUESTION

In patients with operable esophageal cancer, does neoadjuvant chemoradiotherapy or chemotherapy given before surgery increase survival?

METHODS

Data sources: Reference lists of previous systematic reviews, MEDLINE, EMBASE/Excerpta Medica, Cancerlit, and lists of conference abstracts (1980 to 2006).

Study selection and assessment: English-language randomized controlled trials (RCTs) that compared neoadjuvant chemoradiotherapy or chemotherapy followed by surgery with surgery alone in the initial management of operable esophageal cancer and did intention-to-treat analysis. 10 RCTs (n = 1209, median age 62 y, range 28 to 83 y) of neoadjuvant chemoradiotherapy and 8 RCTs (n = 1724, median age 63 y, range 30 to 84 y) of neoadjuvant chemotherapy met the selection criteria.

Outcomes: Overall survival.

MAIN RESULTS

Chemoradiotherapy improved overall survival, but the effect of chemotherapy was smaller and of borderline statistical significance (Table). Chemoradiotherapy was effective for patients with squamous cell carcinoma (SCC) (hazard ratio [HR] for death 0.84, 95% CI 0.71 to 0.99) and with adenocarcinoma (HR 0.75, CI 0.59 to 0.95). In patients with SCC, concurrent chemoradiotherapy improved survival (HR 0.76, CI 0.59 to 0.98) but sequential chemoradiotherapy did not (HR 0.90, CI 0.72 to 1.03). Neoadjuvant chemotherapy improved survival for adenocarcinoma (HR 0.78, CI 0.64 to 0.95) but not for SCC (HR 0.88, 0.75 to 1.03) or mixed tumors (HR 1.07, CI 0.87 to 1.32).

CONCLUSION

Neoadjuvant chemoradiotherapy and chemotherapy improve survival in patients with operable esophageal cancer.

Source of funding: Australian National Health and Medical Research Council; New South Wales Cancer Institute.

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Overall survival with neoadjuvant therapy plus surgery vs surgery alone for esophageal cancer at 2 years (median follow-up 4 years)*

Type of neoadjuvant therapy	Number of trials (n)	Neoadjuvant therapy plus surgery	Surgery alone	RBI (95% CI)	NNT (CI)
Chemoradiotherapy	10 (1209)	39%	33%	18% (6 to 32)	17 (10 to 48)
Chemotherapy	8 (1724)	36%	33%	8.8% (0 to 18)	Not significant

*Abbreviations defined in Glossary. Neoadjuvant therapy survival rates, RBI, NNT, and CI calculated from hazard ratios in article.

COMMENTARY

Although previous meta-analyses have suggested survival benefits with neoadjuvant concurrent chemoradiation for esophageal cancer, its role is still debated because of the heterogeneity of radiation doses and surgical results in randomized trials.

Gebski and colleagues conducted a meta-analysis of 18 randomized trials that compared neoadjuvant therapy with surgery alone. This review, which is the most comprehensive to date, included individual patient data from 2 trials and unpublished results. The findings of the meta-analysis are statistically robust and indicate that neoadjuvant chemoradiotherapy and, to a lesser degree, neoadjuvant chemotherapy lead to improved survival, particularly in patients with adenocarcinoma. However, the authors underscored the survival benefit shown by adjuvant chemoradiotherapy in gastroesophageal junction cancer (1).

Modern staging methods, including positron emission tomography and endoscopic ultrasonography, improve patient selection for neoadjuvant protocols. Advanced radiation technologies and novel chemotherapeutic agents have better outcomes than those reported by the older studies included in this meta-analysis. Therefore, the true benefit of neoadjuvant chemoradiotherapy may be underestimated.

Neoadjuvant chemoradiotherapy should now be regarded as the treatment of choice for esophageal adenocarcinoma. Future trials should incorporate targeted agents based on tumor genetic profiles into neoadjuvant protocols.

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Review: Magnetic resonance imaging is an accurate test for diagnosing foot osteomyelitis

Kapoor A, Page S, LaValley M, Gale DR, Felson DT. **Magnetic resonance imaging for diagnosing foot osteomyelitis: a meta-analysis.** Arch Intern Med. 2007;167:125-32.

Clinical impact ratings: Endocrinology ★★★★★☆☆ Infectious Disease ★★★★★☆☆

QUESTION

How accurate is magnetic resonance imaging (MRI) for diagnosing foot osteomyelitis?

METHODS

Data sources: MEDLINE, EMBASE/Excerpta Medica (to June 2006), reference lists, and experts in the field.

Study selection and assessment: English-language studies that evaluated the diagnostic test performance of MRI in mainly adult patients (≥ 80% of patients ≥ 16 y of age) with foot infection or suspected osteomyelitis of the foot or ankle, using bone biopsy (histologic analysis or culture) as the reference standard. 16 studies (n = 485, mean age range 46 to 66 y) met the selection criteria.

Outcomes: Sensitivity, specificity, diagnostic odds ratio, and positive and negative likelihood ratios (LRs).

MAIN RESULTS

Diagnostic test characteristics for MRI in diagnosing foot osteomyelitis are shown in the Table. MRI was a more accurate diagnostic test than technetium-99m bone scanning, plain radiography, or white blood cell scanning (Table). With a pretest probability for osteomyelitis of 50% (prevalence in the studies ranged from 32% to 89%), a positive MRI would result in a posttest probability of 84%, whereas a negative MRI would result in a posttest probability of 11%.

CONCLUSION

Magnetic resonance imaging has good diagnostic performance for foot osteomyelitis.

Source of funding: National Institutes of Health.

For correspondence: Dr. A. Kapoor, Boston University, Boston, MA, USA. E-mail alok.kapoor@bmc.org.

Diagnostic accuracy of magnetic resonance imaging (MRI) for foot osteomyelitis with bone biopsy as the reference standard*

Tests	Number of studies (n)	Sensitivity (range)	Specificity (range)	Diagnostic odds ratio (95% CI)†	+LR	−LR
MRI	16 (485)	90% (77 to 100)	83% (40 to 100)	42 (15 to 120)	5.1	0.12

Comparisons‡		Diagnostic odds ratio (CI)†	
		MRI	Comparator
MRI vs technetium-99m bone scanning	7 (163)	150 (55 to 411)	3.6 (1 to 13)
MRI vs plain radiography	9 (224)	82 (14 to 466)	3.3 (2 to 5)
MRI vs white blood cell scanning	3 (63)	120 (62 to 234)	3.4 (0.2 to 62)

*Abbreviations and diagnostic terms defined in Glossary.
†Diagnostic odds ratio = (true positive x true negative)/(false positive x false negative).
‡In studies that compared 2 diagnostic techniques in the same patients.

COMMENTARY

The diagnosis of osteomyelitis in patients with diabetes and foot infections has important clinical implications. It dictates much longer antibiotic treatment and sometimes earlier surgical intervention (1). The review and meta-analysis by Kapoor and colleagues showed that MRI has high specificity and even higher sensitivity for diagnosing osteomyelitis and compares favorably with other imaging methods. However, the figures given in the review might be overestimates. Studies with better methodology showed poorer performance. The prevalence of osteomyelitis in the included studies was higher than the rate of 20% observed in patients with a foot infection in an outpatient diabetes practice (2). Such a difference might raise doubt about whether the spectrum of patients enrolled in the studies is representative of different clinical settings.

In clinical practice, patients with a positive plain radiograph or with bone exposed by examination or probing are managed as having osteomyelitis (1–4); it would be informative to know the performance of MRI in patients who score negative for these 2 clinical features.

Nevertheless, the original studies and the review by Kapoor and colleagues show convincingly that MRI is the most accurate imaging procedure for diagnosing foot osteomyelitis in patients with diabetes. MRI should be considered in patients who have foot infection with no bone exposed, have been treated for 2 to 3 weeks with little clinical improvement, and have negative or inconclusive plain radiographs (1). In each medical setting, one needs to consider not only the cost-effectiveness of the test but also the availability of MRI for patients with diabetes and foot infections (a relatively common problem), given the existing infrastructure. In our setting (a large health maintenance organization), it will probably be the exceptional (rather than the common) patient who will undergo MRI for this indication.

Future research should address the question of whether managing patients with diabetes and foot infections using MRI leads to better outcomes.

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Review: Commercial interferon-γ release assays have high specificity but suboptimal sensitivity for detecting latent TB

Menzies D, Pai M, Comstock G. **Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research.** Ann Intern Med. 2007;146:340-54.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Infectious Disease ★★★★★★☆ Trop & Travel Med ★★★★★★☆ Public Health ★★★★★★☆

QUESTION

In healthy or immunosuppressed persons, what is the diagnostic accuracy of commercially available interferon-γ release assays (IGRAs) for diagnosing latent tuberculosis (TB)?

METHODS

Data sources: MEDLINE (to October 2006), bibliographies of relevant studies, and handsearches of the *International Journal of Tuberculosis and Lung Disease.*

Study selection and assessment: English-language studies that used QuantiFERON (QFT) or Elispot tests with overnight incubation of peripheral blood lymphocytes stimulated with RD1 antigens. No gold standard exists for testing latent TB. Studies of sensitivity had to include persons with active TB or contact with a person with TB (exposure had to be graded with ≥ 2 categories). Studies of specificity had to include healthy lifelong residents of low-incidence countries who had a mean age < 40 years and did not have occupational, travel, or other exposure to TB. Studies were excluded if use of a second test depended on the results of a first test. The review included 22 studies evaluating sensitivity with active TB as a surrogate for latent TB, 10 studies evaluating sensitivity with gradient of exposure as an indication of latent TB, and 11 studies evaluating specificity. The quality of study methods was assessed (e.g., blinding and microbiologic or histologic confirmation of diagnosis). Studies were pooled using a fixed-effects model.

Outcomes: Sensitivity and specificity.

MAIN RESULTS

In persons with newly diagnosed active TB, pooled sensitivity was 71% for tuberculin skin testing, 76% for QFT, and 88% for Elispot tests (Table). In persons from low-incidence countries, pooled specificity was 66% for tuberculin skin testing, 97% for QFT, and 92% for Elispot (Table). In studies that used gradient of exposure to indicate latent TB, the prevalence of positive test results in the high-exposure group ranged from 22% to 100% for Elispot (7 studies) and from 44% to 74% for QFT (3 studies). Relative to the tuberculin skin test, a greater prevalence of positive IGRA test results among highly exposed persons was seen for 3 of 7 Elispot studies and 1 of 3 QFT studies.

CONCLUSION

Commercial interferon-γ release assays have high specificity but less than optimal sensitivity for detecting latent tuberculosis in healthy or immunosuppressed persons.

Source of funding: No external funding.

For correspondence: Dr. D. Menzies, Montreal Chest Institute, Montreal, Quebec, Canada. E-mail dick.menzies@mcgill.ca.

Commercially available interferon-γ release assays for detecting latent TB*

Test	Number of studies	Pooled sensitivity (95% CI)†	Number of studies	Pooled specificity (CI)
Tuberculin skin testing	14	71% (65 to 74)	8	66% (46 to 86)
QuantiFERON	13	76% (70 to 83)	9	97% (95 to 99)
Elispot or T-SPOT.TB	12	88% (81 to 95)	4	92% (88 to 95)

*TB = tuberculosis. Diagnostic terms defined in Glossary. Studies were pooled using a fixed-effects model.
†Patients with active TB were used as surrogates for latent TB.

COMMENTARY

Despite the availability of effective treatment methods, TB continues to be a major public health problem. About one third of the world's population is estimated to be infected with *Mycobacterium tuberculosis* (1); this huge burden of latent TB infection poses a global threat to TB control. Latent TB infection is also an occupational risk for health care workers who are constantly exposed to infectious patients. Prophylaxis with isoniazid is the accepted method of treatment, and its appropriate use is dependent on accurate diagnosis of latent TB infection. Tuberculin skin testing remains the mainstay of diagnosis of latent TB in the world, regardless of endemicity.

The new IGRAs seem to be promising alternatives to the tuberculin skin test for latent TB diagnosis. These commercially available assays are T-cell–based, enzyme-linked immunosorbent assays that measure antigen-specific production of interferon-γ. They overcome the limitations of tuberculin skin testing, including crossreactivity to Bacille Calmette-Guérin, booster effect (anamnestic recall of immunity due to repeated testing), and false-negative results in patients with active TB and immunocompromised (HIV) persons. Despite these advantages, the newer IGRAs do not distinguish between latent and active TB, which is an ongoing challenge in clinical practice. Due to the lack of a gold standard for diagnosis of latent TB, active TB has been used as a surrogate for latent infection.

The review by Menzies and coworkers suggests that IGRA response generally decreased with treatment in patients with active TB. This finding could have serious implications for using the test to diagnose latent TB in populations where empirical treatment for tuberculosis is widespread. As these assays are resource-intensive, they would be more useful in low-incidence, high-income settings and are of limited value in highly endemic, resource-limited settings.

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Reference

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Absolute risk for subsequent fracture was similar in women and men

Center JR, Bliuc D, Nguyen TV, Eisman JA. **Risk of subsequent fracture after low-trauma fracture in men and women.** JAMA. 2007;297:387-94.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Geriatrics ★★★★★☆☆

QUESTION

What is the risk for subsequent fracture after initial low-impact fracture in women and men?

METHODS

Design: Inception cohort followed for median 16 years in women and 15 years in men (Dubbo Osteoporosis Epidemiology Study).

Setting: Community study in Dubbo, New South Wales, Australia.

Patients: 1242 patients ≥ 60 years of age (905 women [mean age 78 y] and 337 men [mean age 77 y] at time of incident fracture) who had an initial low-impact fracture (caused by a fall from a standing height or less) between January 1989 and April 2005. Patients with skull, finger, and toe fractures or an underlying condition that could predispose to pathologic fracture were excluded.

Prognostic factors: Smoking, alcohol, and dietary calcium intake; comorbid conditions and medications; anthropomorphic measurements; bone mineral density of the lumbar spine and femoral neck; quadriceps strength; and body sway.

Outcomes: Subsequent fracture.

MAIN RESULTS

Among 905 women with initial fracture, 253 had a subsequent fracture over 4076 person-years (median 3.25 y) of follow-up. Among 337 men with initial fracture, 71 had a subsequent fracture over 1248 person-years (median 2.13 y) of follow-up. Absolute refracture risks were similar between women and men (62/1000 person y, 95% CI 55 to 70/1000 person y and 57/1000 person y, CI 45 to 72/1000 person y, respectively), and these rates persisted across all age groups and most initial fracture types. Given the smaller number of men with initial fracture, the relative risk for refracture was almost twice as high in men as in women (3.47 [CI 2.69 to 4.48] vs 1.97 [CI 1.71 to 2.26]). For women and men, the refracture risk was equivalent to or greater than the initial fracture risk for a woman 10 years older. Using multivariate analysis, the adjusted hazard ratios for refracture showed that greater body sway (men 1.56, CI 1.01 to 2.41; women 1.00, CI 0.83 to 1.21), lower calcium intake (men 2.22, CI 1.37 to 3.58; women 1.09, CI 0.95 to 1.25), and lower levels of physical activity (men 1.81, CI 1.17 to 2.82; women 1.01, CI 0.85 to 1.19) were more important factors for men than for women, whereas age was more important for women than for men (women 1.33, CI 1.10 to 1.61; men 1.06, CI 0.65 to 1.73). Smoking was important for both, but the magnitude was greater in men than in women (men 2.43, CI 0.99 to 5.94; women 1.43, CI 1.03 to 2.00).

CONCLUSIONS

After initial low-impact fracture, women and men 60 years of age had similar absolute risks for subsequent fracture, across all age groups and most initial fracture types. Men had a refracture risk equivalent to that of a woman 10 years older.

Sources of funding: National Health & Medical Research Council; Merck Sharp & Dohme; Eli Lilly; GE Lunar Corporation.

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COMMENTARY

Previous studies have shown increased risk for subsequent fracture after hip, vertebral, and wrist fractures (1), but the study by Center and colleagues is the first to comprehensively examine the subsequent risk for all fracture types after an initial low-impact fracture. The authors found a relatively high risk for subsequent fracture among both men and women with initial fracture. Given that few persons are screened or treated for osteoporosis after a fracture (2), this is not necessarily surprising.

While the numbers of secondary fractures are substantial, from the perspective of a patient having his or her first fracture, the authors may have overstated the absolute risk for subsequent fracture for survivors by not accounting for the competing risk for death (3). Patients with such osteoporotic fractures as hip fractures have an increased risk for dying (4), such that they would not have the "opportunity" to sustain another fracture. Thus, a better understanding of predictors of mortality after a fracture is needed to accurately differentiate individuals at risk for dying from those who are likely to live long enough to have second fractures.

It is important to note that the authors also found that of persons who had a second fracture, about 60% of women and 50% of men had the second fracture > 2 years after the initial fracture. This has significant clinical implications. Many second fractures occur > 6 months after the initial fracture; thus, there is time to implement such secondary prevention measures as fall prevention, vitamin D supplementation, or pharmacologic interventions. Bisphosphonates are currently being studied in secondary prevention of fractures (5).

This study underscores the often-forgotten fact that a fracture is not a normal outcome of aging, but a potent risk factor for future fracture. It is strongly recommended that both women and men with fracture be vitamin D–replete and be considered for pharmacologic treatment, which may prevent second fractures.

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Conventional antipsychotic drugs increased risk for death more than did atypical antipsychotic drugs in elderly patients

Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS. **Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients.** CMAJ. 2007;176:627-32.

Clinical impact ratings: Mental Health ★★★★★★★ GIM/FP/GP ★★★★★☆☆ Hospitalists ★★★★★☆☆ Geriatrics ★★★★★★☆

QUESTION

In elderly patients, is the use of conventional or atypical antipsychotic drugs (APDs) associated with increased risk for death?

METHODS

Design: Cohort study.

Setting: British Columbia, Canada.

Patients: 37 241 patients ≥ 65 y of age who filled new (index) prescriptions of oral conventional (n = 12 882, mean age 80 y, 60% women) or atypical (n = 24 359, mean age 80 y, 65% women) APDs, used ≥ 1 medical service, and filled ≥ 1 prescription in the two 6-month intervals before the index date. Exclusion criteria were cancer and use of APDs in the year before the index date. The atypical APDs evaluated were risperidone, quetiapine, olanzapine, and clozapine; conventional APDs were loxapine, haloperidol, chlorpromazine, trifluoperazine, thioridazine, pimozide, promazine, perphenazine, fluphenazine, mesoridazine, and thiothixene.

Risk factors: Use of APDs, dose or duration of drug, dementia status, and residence in a nursing home. Results were adjusted for year, age, sex, race, diabetes, coronary or cardiovascular diseases, HIV, cancer, dementia, psychotic or psychiatric disorders, psychiatric or anticholinergic drug use, number of medications, hospitalization, and residence in a nursing home.

Outcomes: All-cause mortality within 180 days after the start of APD therapy.

MAIN RESULTS

Multivariate analysis showed that within the first 180 days of APD therapy, the conventional group had more deaths than did the atypical group (14% vs 9.6%; Table). Higher doses of conventional APDs and APD therapy in the first 40 days were associated with the greatest increases in risk for death (Table). Regardless of dementia status or residence in a nursing home, the conventional group had more deaths than did the atypical group (Table).

CONCLUSION

Use of conventional antipsychotic drugs increased risk for death more than did use of atypical antipsychotic drugs in elderly patients.

Sources of funding: DEcIDE Research Network and National Institute on Aging.

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Risk factors for all-cause mortality within 180 days after the start of conventional vs atypical antipsychotic drug (APD) therapy in elderly patients*

Risk factors	Adjusted hazard ratio† (95% CI)
Any conventional APD	1.32 (1.23 to 1.42)
High-dose conventional APD	1.67 (1.50 to 1.86)
Low-dose conventional APD	1.23 (1.14 to 1.33)
< 40 d after start of APD therapy	1.60 (1.42 to 1.80)
40 to 79 d after start of APD therapy	1.31 (1.14 to 1.51)
80 to 180 d after start of APD therapy	1.18 (1.06 to 1.31)
Dementia	1.26 (1.01 to 1.56)
No dementia	1.30 (1.21 to 1.40)
In a nursing home	1.25 (1.12 to 1.40)
Not in a nursing home	1.35 (1.23 to 1.49)

*CI defined in Glossary.

†Adjusted for year, age, sex, race, diabetes, coronary or cardiovascular diseases, HIV, cancer, dementia, psychotic or psychiatric disorders, psychiatric or anticholinergic drug use, number of medications, hospitalization, and residence in nursing home.

COMMENTARY

Safety concerns regarding APDs have been long-standing, but warnings from drug regulatory bodies have heightened attention on atypical APDs. In a meta-analysis by Schneider and colleagues (1), higher risk for death was associated with use of atypical APDs compared with placebo (odds ratio [OR] 1.54, 95% CI 1.06 to 2.23). Conventional APDs are also associated with increased risk. Pooled data from 2 studies showed a nonsignificant relative risk (RR) increase for death in patients taking haloperidol compared with placebo (1).

In the study by Schneeweiss and colleagues, conventional APDs were associated with a 32% increased risk for death compared with atypical APDs, consistent with results from a similar study of Medicaid beneficiaries (RR 1.37, CI 1.27 to 1.49) (3). The finding is further supported by a positive dose–response relationship, although it is difficult to determine the actual dose of APD used by patients from administrative data.

Critics of observational studies often cite the inability of statistical methods to control for confounding factors. Channeling bias is particularly difficult to overcome; if physicians selectively prescribed conventional APDs to patients who were more likely to die, an observed increased risk for mortality may not be attributable to drug exposure. Schneeweiss and colleagues used several analyses to control for confounding factors. Examination of individual drugs showed highest risk for death associated with haloperidol compared with risperidone (OR 2.14, CI 1.86 to 2.45). This is higher than the placebo-controlled point estimate for haloperidol from the meta-analysis by Schneider and colleagues (1) but falls within the reported CI. The higher rate may indicate some channeling bias.

Since randomized evaluation of death associated with conventional APDs is unlikely to be forthcoming, observational data can assist in clinical decision making. Given the serious nature of adverse outcomes, the burden of evidence should be to prove superior safety rather than criticize evidence showing equivalence in toxicity. If APDs are required, the side effect profile and pharmacologic properties of each drug should be considered in the context of the individual patient. Given the balance of evidence, conventional APDs should be considered to have at least the same, if not higher, risk for death as atypical APDs.

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Aspirin was cost-effective for primary prevention of cardiovascular events in older women at moderate risk

Pignone M, Earnshaw S, Pletcher MJ, Tice JA. **Aspirin for the primary prevention of cardiovascular disease in women: a cost-utility analysis.** Arch Intern Med. 2007;167:290-5.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Cardiology ★★★★★★☆

QUESTION

Is aspirin cost-effective for primary prevention of cardiovascular (CV) events in women?

METHODS

Design: Cost–utility analysis using a Markov model from the perspective of a third-party payer and a lifetime time horizon.

Setting: United States.

Patients: A hypothetical cohort of women assumed to be 65 years of age with moderate 10-year risk for CV events (estimated 7.5% risk for coronary heart disease and 2.8% risk for stroke). Systolic blood pressure was 120 mm Hg; total cholesterol level was 184 mg/dL (4.77 mmol/L); high-density lipoprotein cholesterol level was 40 mg/dL (1.04 mmol/L). They were assumed to be nonsmokers and not to have diabetes or atrial fibrillation.

Intervention: Aspirin or no aspirin.

Outcomes: Cost per quality-adjusted life-year (QALY) gained. Costs were estimated from mixed populations of men and women, derived from published studies and several recent national databases, and expressed in 2005 U.S. dollars with a 3% annual discount rate. Effectiveness estimates were obtained from a meta-analysis of randomized controlled trials (RCTs); clinical probability estimates were derived from National Vital Statistics life tables, Framingham risk equations, population-based studies, and systematic reviews.

MAIN RESULTS

In the base-case analysis, aspirin use in women at moderate risk for CV events led to a cost–utility ratio of $13 300 per QALY gained. The mean cost for women receiving aspirin was greater than for those not receiving aspirin ($3145 vs $3069) for a difference of 0.006 QALYs gained in the aspirin group. One-way sensitivity analysis showed that the model was sensitive to the patient's age, daily pill consumption, risk for CV events, risk reduction with aspirin for ischemic stroke or myocardial infarction, risk reduction with secondary prevention, excess risk for gastrointestinal bleeding or death from gastrointestinal bleeding, and risk for hemorrhagic stroke. Probabilistic sensitivity analysis found that this estimate was most sensitive to the effects of aspirin on rates of myocardial infarction or stroke. For women whose stroke risk was doubled due to hypertension, aspirin was more effective and less costly than no treatment.

CONCLUSION

In older women at moderate risk for cardiovascular disease, aspirin was cost-effective for primary prevention of cardiovascular events.

Sources of funding: Bayer and Center for Health Promotion Economics.

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COMMENTARY

In 1988, the Physicians' Health Study showed a 44% relative risk reduction in first myocardial infarction (MI) in men taking aspirin. Despite no difference in physiologic response to aspirin by sex, the effectiveness of aspirin in preventing a first MI in women has not been proven by RCTs. In the more recent Women's Health Study (WHS), aspirin led to a nonsignificant reduction in the composite endpoint of major CV events (nonfatal MI, nonfatal stroke, or CV death) but caused a significant decrease in ischemic stroke as well as stroke and MI in the subgroup of women > 65 years of age (1). This was at the expense of increased gastrointestinal bleeding requiring transfusion (relative risk 1.40, 95% CI 1.07 to 1.83) (1).

Pignone and colleagues examined the cost-effectiveness of aspirin for primary prevention of CV events in women. Both benefit and cost-effectiveness, as expected, were highly contingent on the woman's baseline CV risk. In 65-year-old women with a 10% 10-year risk for MI or stroke, the cost-effectiveness of aspirin was estimated at $13 300 per QALY gained. A probabilistic sensitivity analysis to assess the robustness of the results showed a 73% chance that aspirin is beneficial but only a 35% chance of cost-effectiveness at the traditional threshold of < $50 000 per QALY gained.

This analysis highlights the limitations of the underlying data. The WHS is the only large primary prevention trial studying aspirin in women. Many of the women in the WHS were considerably younger (mean age 55 y) than the base-case age of Pignone and colleagues' study, but 10% (n = 4107) were ≥ 65 years. The WHS tested aspirin at a dose of 100 mg every other day. Meta-analysis (mainly secondary prevention) suggests an optimal dose range of 75 to 150 mg/d with less effect at lower doses (2).

According to the American Heart Association and U.S. Preventive Services Task Force recommendations, it is reasonable to limit primary prevention use of aspirin in women to those with ≥ 10% baseline 10-year risk for a first coronary event (vs > 6% in men).

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A clinical risk score identified high-risk patients with chest pain but no ST-segment deviation and normal troponin levels

Sanchis J, Bodí V, Núñez J, et al. **A practical approach with outcome for the prognostic assessment of non-ST-segment elevation chest pain and normal troponin.** Am J Cardiol. 2007;99:797-801.

Clinical impact ratings: Emergency Med ★★★★★★☆ GIM/FP/GP ★★★★★☆☆ Hospitalists ★★★★★★☆ Cardiology ★★★★☆☆☆

QUESTION

In patients with suspected acute coronary syndromes (ACSs) but no ST-segment deviation or important increases in troponin levels, does a clinical risk score (CRS) identify patients at increased risk for death or myocardial infarction (MI) at 1 month and in the longer term?

METHODS

Design: Prospective cohort study.

Setting: Emergency department (ED) of a university hospital in Spain.

Patients: Patients presenting to the ED with chest pain of possible coronary origin were evaluated by a cardiologist using a protocol consisting of clinical history, a previously developed chest pain questionnaire, electrocardiogram, serial troponin I determination, and early exercise testing in eligible patients. Patients with ST-segment elevation, new left branch bundle block, history of nonischemic heart disease, or heart failure at admission were excluded. Based on the results of the tests, the patients were divided into 3 cohorts: those with troponin increases (n = 552, mean age 68 y, 69% men), those with ST-segment depression but normal troponin levels (n = 106, mean age 68 y, 68% men), and those with no ST-segment deviation and normal troponin levels. The last cohort was further divided, based on a CRS that was previously derived and validated in the same group of patients, into those at high risk for a poor prognosis (n = 158, mean age 70 y, 71% men) and those at low risk (n = 633, mean age 62 y, 66% men). Patients received appropriate treatment at their physician's discretion.

Description of prediction guide: The CRS (range 0 to 6) categorized patients into low- (score < 3) or high-risk (score ≥ 3) groups. The CRS was a summation of 5 clinical variables: score ≥ 10 points on the chest pain questionnaire, ≥ 2 episodes of chest pain in < 24 hours, age ≥ 67 years, insulin-dependent diabetes (2 points), and previous percutaneous coronary angioplasty.

Outcomes: A composite endpoint of death or nonfatal MI at 30 days and longer term (median duration of follow-up 26 mo).

MAIN RESULTS

Risk for death or MI, at both 30 days and longer term, was lowest in the group with no ST-segment deviation and normal troponin levels that was categorized by the CRS as low risk; the other 3 groups did not differ (Table).

CONCLUSION

A simple clinical risk score identified a subgroup of high-risk patients with chest pain, non–ST-segment deviation, and normal troponin levels for whom the outcome was similar to that of patients with increased troponin levels or ST-segment depression.

Sources of funding: Instituto de Salud Carlos III and Fundación Española del Corazón.

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Composite endpoint of death or myocardial infarction in patients with non–ST-segment elevation chest pain, categorized by presence or absence of ST-segment depression and increased troponin levels and, in the absence of both, by risk score*

Risk group	Incidence at 30 d (95% CI)	Adjusted odds ratio at 30 d (CI)†	Incidence at median 26 mo (CI)	Adjusted hazard ratio at median 26 mo (CI)†
Low risk (score < 3) non–ST-segment depression, normal troponin	1.7% (0.9 to 3.1)	0.2 (0.1 to 0.4)	9.3% (7.2 to 12)	0.4 (0.3 to 0.6)
High risk (score ≥ 3) non–ST-segment depression, normal troponin	10.8% (6.4 to 17)	0.9 (0.5 to 1.7)	26% (19 to 34)	0.7 (0.5 to 1.1)
ST-segment depression, normal troponin	6.6% (2.7 to 13)	0.6 (0.3 to 1.4)	30% (22 to 40)	1.2 (0.8 to 1.7)
Troponin increase	9.4% (7.1 to 12)	1 (reference)	25% (21 to 29)	1 (reference)

*CI defined in Glossary.

†Odds ratios and hazard ratios adjusted for other risk factors, such as age, hypertension, diabetes, and previous myocardial infarction.

COMMENTARY

Accurate risk stratification is the cornerstone of the often-challenging task of evaluating a patient with suspected ACS. The difficulty is heightened by imperfect biomarkers, the limited utility of a normal electrocardiogram, and the fact that most patient presentations ultimately "rule out" ACS. Discriminating between patients at high and low risk for short-term adverse events is crucial for deciding which patients require aggressive treatment strategies (early percutaneous coronary intervention) and which patients can be safely discharged.

The work by Sanchis and colleagues points to the potential value of a 5-item CRS in identifying high-risk (and low-risk) patients among those who are troponin-negative and do not demonstrate ST-segment deviations. However, these findings are constrained by a relatively narrow, single-center validation, reliance on composite endpoints as outcomes for both follow-up periods, the apparent lack of blinding in outcome assessment and rule interpretation, and the relatively wide confidence intervals around the adverse event rates in the low-risk group (upper 95% confidence limit 3% at 30 d).

Fortunately, there is a more accurate, discriminating, and widely validated CRS that can provide useful guidance. The easy-to-use and intuitive 7-item Thrombolysis In Myocardial Infarction (TIMI) risk score, derived and initially validated in 2 large populations of patients with ACS (in contrast to the CRS of Sanchis and colleagues, which was derived in patients with acute chest pain of uncertain coronary origin), is the most well-studied CRS in ACS, showing utility in patients with a clear diagnosis, as well as those with undifferentiated chest pain (1–3). Although not sufficiently sensitive to "rule-out" ACS and discharge patients on its own, the TIMI score provides meaningful and graded measures of risk that can serve as powerful supplements to clinical judgment.

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3. **Pollack CV Jr., Sites FD, Shofer FS, Sease KL, Hollander JE.** Acad Emerg Med. 2006;13:13-8.

The journals that are reviewed, and the criteria for selecting articles from these journals for inclusion in *ACP Journal Club,* are set out in the Purpose and Procedure in each issue. All articles that meet our criteria in the reviewed journals are cited in *ACP Journal Club,* but there is not enough space to abstract them all. The following articles passed all criteria but were not abstracted because, in the judgment of the editors, their findings were less widely applicable to clinical practice in internal medicine.

THERAPEUTICS

Khush KK, Waters DD, Bittner V, et al. **Effect of high-dose atorvastatin on hospitalizations for heart failure: subgroup analysis of the Treating to New Targets (TNT) study.** Circulation. 2007;115:576-83.
GIM/FP/GP ★★★★★☆☆
Hospitalists ★★★★☆☆☆
Cardiology ★★★★★★☆

Konstam MA, Gheorghiade M, Burnett JC Jr, et al. **Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial.** JAMA. 2007;297:1319-31.
Hospitalists ★★★★★☆☆ **Cardiology** ★★★★★★☆

Remme WJ, Torp-Pedersen C, Cleland JG, et al. **Carvedilol protects better against vascular events than metoprolol in heart failure: results from COMET.** J Am Coll Cardiol. 2007;49:963-71.
Hospitalists ★★★★★★☆ **Cardiology** ★★★★★★☆

Recio-Mayoral A, Chaparro M, Prado B, et al. **The reno-protective effect of hydration with sodium bicarbonate plus N-acetylcysteine in patients undergoing emergency percutaneous coronary intervention: the RENO Study.** J Am Coll Cardiol. 2007;49:1283-8.
Cardiology ★★★★★★☆ **Nephrology** ★★★★★★★

Montalescot G, Antoniucci D, Kastrati A, et al. **Abciximab in primary coronary stenting of ST-elevation myocardial infarction: a European meta-analysis on individual patients' data with long-term follow-up.** Eur Heart J. 2007;28:443-9.
Cardiology ★★★★★☆☆

Rocca HP, Kaiser C, Pfisterer M. **Targeted stent use in clinical practice based on evidence from the BAsel Stent Cost Effectiveness Trial (BASKET).** Eur Heart J. 2007;28:719-25.
Cardiology ★★★★★★☆

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Cardiology ★★★★★☆☆

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Hospitalists ★★★★★★☆ **Cardiology** ★★★★★★☆

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Cardiology ★★★★★★☆

Deedwania P, Stone PH, Bairey Merz CN, et al. **Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE).** Circulation. 2007;115:700-7.
GIM/FP/GP ★★★★★★☆
Cardiology ★★★★★☆☆ **Geriatrics** ★★★★★☆☆

Goldstein JA, Gallagher MJ, O'Neill WW, et al. **A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain.** J Am Coll Cardiol. 2007;49:863-71.
Emergency Med ★★★★★★☆
Cardiology ★★★★★☆☆

Ferreira-Gonzalez I, Dos-Subira L, Guyatt GH. **Adjunctive antiarrhythmic drug therapy in patients with implantable cardioverter defibrillators: a systematic review.** Eur Heart J. 2007;28:469-77.
Cardiology ★★★★★☆☆

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Cardiology ★★★★★★☆ **Nephrology** ★★★★★★☆

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GIM/FP/GP ★★★★★☆☆
Cardiology ★★★★★☆☆ **Geriatrics** ★★★★★★☆
Oncology ★★★★★☆☆

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GIM/FP/GP ★★★★★★☆
Cardiology ★★★★★☆☆

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Neurology ★★★★★★☆

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Hospitalists ★★★★★☆☆ **Neurology** ★★★★★★☆

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GIM/FP/GP ★★★★★★★
Pulmonology ★★★★★★☆

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GIM/FP/GP ★★★★★★☆
Pulmonology ★★★★★☆☆

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Allerg & Immunol ★★★★★★☆
Pulmonology ★★★★★★★

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GIM/FP/GP ★★★★★★☆
Allerg & Immunol ★★★★★★☆
Pulmonology ★★★★★☆☆

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Hospitalists ★★★★☆☆☆
Pulmonology ★★★★★★☆

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Pulmonology ★★★★★★☆

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Cardiology ★★★★★★☆ **Nephrology** ★★★★★★★

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Hematol/Thrombo ★★★★☆☆☆
Nephrology ★★★★★★☆

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Endocrinology ★★★★★★☆

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Cardiology ★★★★★☆☆
Endocrinology ★★★★★☆☆
Geriatrics ★★★★★★☆ **Neurology** ★★★★★☆☆

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Geriatrics ★★★★★☆☆ **Neurology** ★★★★☆☆☆

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Infectious Disease ★★★★★☆☆

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Gastroenterology ★★★★★★☆
Rheumatology ★★★★★☆☆

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Cardiology ★★★★☆☆☆
Gastroenterology ★★★☆☆☆☆

(continued from page A-8)

6. STATE YOUR ANSWERS TO THE CRITICAL APPRAISAL QUESTIONS ON VALIDITY.

Next, briefly answer the appropriate critical appraisal questions on validity by using the *JAMA Users' Guides to the Medical Literature* (5). Elaborate with some explanation, questions, or concerns if needed. Although it is a bit formulaic to go through each question, it is a good habit to develop, and use of the GATE frame makes it easier (6). Remember, if you suspect bias, consider not only its possible presence, but also its direction, magnitude, and impact on the study's conclusions—not all flaws are fatal. Be cautious not to get lost in the statistics/analysis section. Remember, "Statistics are a tool while study methods rule!"

For a study of the efficacy of therapy, use these questions:

Did the experimental and control groups start out with a similar prognosis?

Were patients randomized?

Was randomization concealed?

Were patients analyzed in the groups to which they were randomized?

Were groups similar regarding known prognostic factors?

Did the experimental and control groups retain a similar prognosis after the study started?

Were patients, clinicians, and outcome assessors aware of group allocation?

Was follow-up complete?

7. SUMMARIZE THE PRIMARY RESULTS.

At last, the results. Some like to present the bottom-line result right away in their presentation titles, similar to the format of *ACP Journal Club*. Alternatively, you can report the results after the descriptors and research question. We find that when browsing through a journal our eyes go from the title (if it sounds interesting) to the conclusions in the abstract. The inner question is, "If this is true (valid), would it be interesting or important to me?" Or, if you prefer to keep people in suspense, save the bottom-line answer for the results:

"Atorvastatin reduced the rate of fatal and nonfatal stroke from 13.1% on placebo to 11.2%, a statistically significant 16% relative reduction in risk over 5 years. There was no difference in overall mortality."

Limit your summary of the results to the primary question and only present secondary results if they are relevant. It is helpful to bring your listeners' eyes to a particular row on a table or a bar on a graph to illustrate your point. You will not insult anyone by taking them by the hand and leading them through the paper. And feel free to play with the numbers.

"As you can see under secondary outcomes in Table 2, major coronary events were reduced by 35% from 5.1% to 3.4%. The primary result suggests an absolute reduction of 2% in fatal and nonfatal stroke so that we would need to treat 50 patients with 80 mg of atorvastatin for 5 years to prevent 1 event, a modest impact."

8. DESCRIBE WHY YOU THINK THE RESULTS CAN OR CANNOT BE APPLIED TO YOUR PATIENTS/SITUATION.

Finish with your assessment of the study's external validity: Can you apply these results to your patients? Better yet, are the patients or setting so different from your own that the findings are useless to you? How much would you have to adjust the study findings to compensate for the differences between the study's patients or setting and your own?

"Would the efficacy be larger or smaller in older patients? In addition, the authors excluded patients at higher risk for hemorrhagic stroke and, in fact, atorvastatin may have increased the risk for hemorrhagic stroke in this study."

9. CONCLUDE WITH YOUR OWN DECISION ABOUT THE UTILITY OF THE STUDY IN YOUR PRACTICE—RESOLVE THE CASE OR QUESTION WITH WHICH YOU BEGAN.

If you started your presentation with a case, be sure to leave time to come back to the case at the end and try to apply the study's findings to your patient or problem. Give your listeners a sense of closure:

"Atorvastatin may modestly reduce the risk for recurrent cerebrovascular events in patients with recent ischemic CVA or TIA. I will offer this medication to such patients but still focus more on those at higher risk for cardiac events."

10. PREPARE A 1-PAGE SUMMARY OF THE OUTLINE ABOVE AS A HANDOUT.

The summary will serve as your notes for the presentation and will help guide the group's attention. It also provides a storable record of the article, similar to critically appraised topics, or CATs (7).

Believe it or not, you can do all this in 10 minutes easy, 5 minutes with very tight editing, and 2 to 3 minutes if you just hit the highlights.

These guidelines have dramatically improved the enthusiasm for, quality of, and attendance at our journal clubs, which have now been running continuously for more than 15 years. Residents are expected to present the paper in 10 minutes, provide a concise 1-page summary using the outline above, and lead a 20-minute discussion on the clinical and methodological issues. As a result, residents have improved both their presentation and critical appraisal skills. In our experience, this approach, familiar to residents because it is parallel to patient case presentations, is easily learned and portable. Developed for a smaller group of primary care residents, the model is now used for all medical residents and fellows. Slides from these workshops are available at www.evidence-basedmedicine.com. We believe this model has contributed to the long-running success of our journal club and made it a lively, relevant, and fun way to simultaneously explore methods and medicine.

Remember, "The conclusions giveth but the methods taketh away!" *Caveat lector*: Reader beware!

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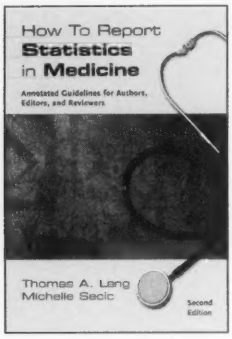

An experienced biostatistician and a clinical investigator read this book, wrote this review together, and think that the book is great. In a nutshell, the first edition was an excellent resource guide to best practices in statistical reporting in the medical literature. The second edition, which is a major reworking and expansion of the first, is even better. The second edition's authors have successfully built on the foundation of the first edition in several ways. For statistician writers, the book offers clear guidelines. For clinical investigators reporting research results, the book offers, in addition to guidelines, a refresher course about biostatistical concepts and methods plus easy-to-read material for potentially unfamiliar areas. For the most part, the authors assume that clinical investigator readers are somewhat familiar with statistical concepts and summarize these succinctly and cogently throughout. The authors have further expanded the material on the most meaningful ways to incorporate statistical methods and results into manuscripts and research thinking.

As a start, the discussion of "Differences between clinical and statistical significance" captures the essence of the basic distinctions between the 2 and how they relate to each other in a rapid-fire short 2 pages. Throughout the book, improved visual techniques include annotated bullet points to highlight examples, methods to check findings, potential problems to which to be alert, and related information. These effectively sensitize the reader to be more critical and proactive in writing and interpreting medical literature while supplying methods for back-of-the-envelope techniques to check statistical results in publications.

Part 1 remains a basic set of guidelines, but the chapter titles and subtitles are even more conceptually meaningful. Part 2 moves beyond reporting pure statistical information to guidelines specific to different study designs. It pulls together all the guidelines that were previously published separately for individual study designs (e.g., randomized trials and cohort and case–control studies) into 1 cohesive section. The authors have taken the annotated reference list of guidelines in the first edition and present them as full individual chapters organized by study design. For example, the reader has the benefit of not only a CONSORT checklist for reporting randomized trials but a well laid out, detailed, and carefully written chapter that includes additional information on handling outlying values, accounting for all observations in study participants, and explaining or dealing with missing data. Part 3 is an entirely new section: "Reporting integrated research methods." This section of 3 chapters summarizes statistical information and guidelines relevant for reporting the statistics associated with evidence synthesis. There are dedicated chapters for systematic reviews, meta-analyses, economic evaluations, decision analyses, and clinical practice guidelines.

The book also contains cues to potential problems, important cautions, and simple errors that writers tend to inadvertently make in their statistical reporting or that we may miss as readers of medical research. For example, page 26 highlights the point that a large relative risk reduction may hide the fact that the absolute risk reduction, which should guide clinical decisions with patients, is actually quite small. Cues on page 67 briefly explain potential fallibilities in subgroup analyses and ways to identify acceptable subgroup analyses.

Overall, the book is a superb guide to reporting statistical results in the medical literature. It has exceptional additional value regarding critically designing studies and appraising the medical literature. The breadth of its audience is large and includes research fellows, investigators at most levels, and all faculty. The second edition has a wonderful mix of text, tables, and figures to promote learning and retention. The statistics are focused on concepts presented in language, tables, and figures that are easy to understand and teach succinctly. Best of all, the book is easy to pick up and put down, to read short sections productively as needs determine and time allows.

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How To Report Statistics in Medicine can be obtained from www.acponline.org for $54.95.

REVIEW: HIGH ALCOHOL INTAKE INCREASES MORTALITY IN BOTH MEN AND WOMEN

Dr. Shekelle's commentary (1) on the article "Alcohol dosing and total mortality in men and women: an updated meta-analysis of 34 prospective studies" in the March/April issue was disappointing and full of the bias that one does not expect to find in a journal that prides itself on letting the evidence do the talking. The chosen title of the commentary, "Review: high alcohol intake increases mortality in both men and women," exposes Dr. Shekelle's insistence on seeing the glass 1/10 empty rather than 9/10 full. Despite the prospective nature of the cohort studies and the overwhelming support for mild-to-moderate alcohol consumption, Dr. Shekelle refuses to acknowledge that there could be a true mortality benefit, instead choosing to state only that "when measured this way, there is a J-shaped association."

The author's 2 criticisms of the study methods are curious: He impugns the practice of measuring self-reported alcohol consumption, despite validation of this technique and proven correlations between self-reported consumption and other markers of alcohol use, such as biochemical markers and patient injuries (2–4). Indeed, the accepted assumption is that self-report may underestimate, rather than overestimate, actual intake. If this is the case, then the mortality benefit may actually extend to relatively higher, rather than lower, amounts of alcohol consumption. Dr. Shekelle's other point, that alcohol consumption may be a marker for other healthy lifestyle behaviors, is an unsupported conjecture that seems farfetched at best.

In all, Dr. Shekelle's personal bias against any alcohol use impairs his ability to interpret strong data in a way that should honestly and meaningfully alter patient care.

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REPLY

I sympathize with Dr. Blum's conclusion that moderate alcohol intake decreases mortality. These data seem consistent and compelling. Why not recommend it? My hesitancy comes from that fact that I have read this story before—too many times, in fact. Vitamin E, hormone replacement therapy, β-carotene, folate: all have been promoted as healthful based on strong, consistent epidemiologic data and a strong, plausible biological rationale. Yet when subjected to the scrutiny of a randomized clinical trial, all of these substances have shown no evidence for the benefits claimed for them, and in some cases, have been shown to actually cause harm (1–4). These findings have made me more skeptical than ever of observational studies of association. I believe that before we can make broad policy conclusions recommending patients take such substances to prevent conditions for which they currently show no evidence of having—particularly substances known to also cause harm (like alcohol)—we simply must have better evidence than that of observational studies. I don't tell patients to stop who, like myself, enjoy a glass of wine with dinner. But I certainly would not tell an abstemious patient that he or she should start drinking in order to prolong their life.

Paul Shekelle, MD, PhD
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THE EVOLVING SCIENCE OF TRANSLATING RESEARCH EVIDENCE INTO CLINICAL PRACTICE

Dr. Scott has provided a nice summary of the barriers to implementing research guidelines (1), although it seems to me he misses 1 important point: The psychology of skepticism, and how skepticism is learned by practitioners. I'll illustrate what I mean by this in the field of new drugs. I think we can agree that the literature about new drugs and their use makes up a considerable proportion of any issue of a major medical journal or continuing education conference. New drugs are extensively studied, and information about their importance and potential benefits is widely disseminated to practitioners. Skepticism is often learned by doctors after the drugs have been released and lauded: Vioxx, Rezulin, Baycol, Avandia, the bisphosphonates: All wonder drugs on release; a couple of years later, you wonder—how did this occur?

Research guidelines are tainted in many practitioners' minds, by association. Drug studies and well-meaning guidelines are often published side-by-side in the same journals. If so many brilliant scientists, so many well-meaning professors, get things so very wrong on p. 1000, how can we tell that the article on p. 1010 is indisputably right? How did the system of health care research blend into the machinery of health promotion, and how does that lead to error? The problem, it seems to me, is in the promotion. Doctors look at guidelines and their promotion as an industry not unlike the drug industry. I think we practicing physicians often ask ourselves, "For my patients, wouldn't it be safer to wait a year or two, to see if the impact of that which is being promoted matches its promise? These patients are, after all, in my care." Fortunately, "caution" is a byword of the way many doctors practice.

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ACP Journal Club's general purpose is to select from the biomedical literature articles that report original studies and systematic reviews that warrant immediate attention by physicians attempting to keep pace with important advances in internal medicine. These articles are summarized in value-added abstracts and commented on by clinical experts. The specific purposes of *ACP Journal Club* are

1. To detect, using prestated criteria, the best original and review articles on the cause, course, diagnosis, clinical prediction, prevention, treatment, or economics of medical disorders managed by internists and related subspecialists and on quality improvement and continuing medical education intervention trials in internal medicine

2. To summarize this literature in the form of "structured abstracts" that describe the objectives, methods, results, and evidence-based conclusions of studies in a reproducible, accurate, and applicable fashion

3. To provide brief commentaries on the context, methods, and clinical applications of the findings of each article by clinicians with a high degree of expertise in the topic of the article who have declared no conflict of interest

4. To disseminate the summaries in a timely fashion to internists and internists-in-training to the extent that resources permit.

The American College of Physicians publishes *ACP Journal Club* bimonthly under the editorship of R. Brian Haynes, MD, PhD, at McMaster University. The Health Information Research Unit of the Department of Clinical Epidemiology and Biostatistics at McMaster University hosts the editorial office for the service. An international editorial board oversees and reviews policy.

More than 100 journals are reviewed to identify articles that meet *ACP Journal Club* criteria. An abridged list of the major journals is included in the Table of Contents of each issue, and a complete list is available from the editorial office. The list is subject to modification based on relative performance of each journal according to the criteria set out below; we also assess journals nominated by readers and editors. Access to foreign-language journals is provided through the systematic reviews we abstract, especially those in the Cochrane Library, which summarizes articles taken from over 800 journals in many languages.

All articles in a journal issue are considered for abstracting if they meet the following basic criteria and category-specific criteria.

BASIC CRITERIA

To meet the basic criteria, all original research and review articles must

- be in English
- be about adult humans
- be about topics, other than descriptive studies of prevalence, that are important to the clinical practice of general internal medicine and its specialties
- analyze the data consistently with the study question.

CATEGORY-SPECIFIC CRITERIA

Studies of prevention or treatment must also include

- random allocation of participants to comparison groups
- follow-up (endpoint assessment) of at least 80% of the participants entering the investigation
- outcome measures of known or probable clinical importance.

Studies of diagnosis must also include

- a spectrum of participants, some but not all of whom have the disorder or derangement of interest
- interpretation of a diagnostic ("gold") standard without knowledge of the test result
- interpretation of the test without knowledge of the diagnostic standard result
- objective diagnostic standard (e.g., laboratory test not requiring interpretation) or current clinical standard for diagnosis (e.g., venography for deep venous thrombosis), preferably with documentation of reproducible criteria for subjectively interpreted diagnostic standard (i.e., report of statistically significant measure of agreement beyond chance among observers).

Studies of prognosis must also include

- inception cohort of individuals, all initially free of the outcome of interest
- follow-up of at least 80% of patients until a major study endpoint occurs or the study ends.

Studies of etiology must also include

- exploration of the relation between exposures and putative clinical outcomes
- clearly identified comparison groups for those at risk for, or having, the outcome of interest (i.e., randomized controlled trial, quasirandomized controlled trial, nonrandomized controlled trial, cohort analytic study with matching or statistical adjustment to create comparable groups, or nested case–control study)
- blinding of observers of outcome to exposure (criterion assumed to be met if outcome is objective, i.e., all-cause mortality, objective test).

Studies of quality improvement or continuing education must also include

- random allocation of participants or units to comparison groups
- follow-up of at least 80% of participants
- an outcome measure of known or probable clinical or educational importance.

Studies of the economics of health care programs or interventions must also include

- an economic question based on comparison of alternatives

- alternate diagnostic or therapeutic services or quality improvement activities compared on the basis of both the outcomes produced (effectiveness) and resources consumed (costs)
- evidence of effectiveness from a study (or studies) that meets the above-noted criteria for diagnosis, treatment, and quality improvement or a systematic review article that also meets the criteria
- results presented in terms of the incremental or additional costs and outcomes of one intervention over another
- a sensitivity analysis if uncertainty exists about the estimates or precision of the measurement.

Studies of clinical prediction guides must also include

- generation of the guide in one or more sets of patients (training set)
- validation in another set of patients (test set)
- the above-noted criteria for treatment, diagnosis, prognosis, or etiology.

Studies of differential diagnosis must also include

- a cohort of patients who present with a similar, initially undiagnosed but reproducibly defined clinical problem
- clinical setting, including the referral filter, is explicitly described
- ascertainment of diagnosis for ≥ 80% of patients using a reproducible diagnostic workup strategy for all patients and follow-up until patients are diagnosed or follow-up of ≥1 month for acute disorders or ≥1 year for chronic or relapsing disorders.

Systematic review articles must also include

- an identifiable description of the methods indicating the sources and methods for searching for articles
- a statement of the clinical topic and the inclusion and exclusion criteria for selecting articles for detailed review
- at least one article that meets the above-noted criteria for treatment, diagnosis, prognosis, clinical prediction, etiology, quality improvement, economics of health care, or differential diagnosis.

These criteria are subject to modification if, for example, it is feasible to apply higher standards that increase the validity and applicability of studies for clinical practice. The objective of *ACP Journal Club* is to abstract only the very best literature, consistent with a reasonable number of articles "making it through the filter."

Articles meeting the criteria set out above are abstracted according to the procedure for more informative abstracts (1), with the following modifications: Abstracts can be up to 425 words in length. Abstracts are reviewed by an expert in the content area covered by the article. A commentary is added to provide the context of the article in the research that has preceded it, any important methodologic problems that affect interpretation, and recommendations for clinical application. The author of the article is given an opportunity to review the abstract and commentary before publication. Because there is not enough space to accommodate abstracts for all articles that meet criteria set forth in Purpose and Procedure, citations for the extra articles will be captured during a search and prefaced with the acronym OAN.

Star Ratings

The stars found immediately adjacent to the citation of each abstracted article are averaged scores for clinical relevance and newsworthiness from the McMaster Online Rating of Evidence (MORE) system. This Internet-based system gathers ratings of new articles, already assessed for scientific merit, from sentinel readers, a panel of over 2000 physicians from around the world. Each sentinel reader assigns ratings to new articles for both relevance and newsworthiness on a scale from 1 to 7. These ratings are then averaged for at least 3 raters for each pertinent discipline. For example, an article about diabetes would be sent to raters in primary care and raters in endocrinology; the ratings from at least 3 raters are averaged for each discipline. Ratings that average 6 or higher help to keep your knowledge up-to-date for essential new evidence.

The areas in which the articles are rated are shown as follows: General Internal Medicine/Family Practice/General Practice (GIM/FP/GP), Hospitalists, Emergency Medicine (Emergency Med), Allergy & Immunology (Allerg & Immunol), Cardiology, Dermatology, Endocrinology, Gastroenterology, Genetics, Geriatrics, Hematology/Thrombosis (Hematol/Thrombo), Infectious Disease, Tropical & Travel Medicine (Trop & Travel Med), Critical Care, Nephrology, Neurology, Oncology, Physical Medicine & Rehabilitation (Phys Med & Rehab), Pulmonology, Rheumatology, Occupational/Environmental Health (Occup/Envir Health), Public Health, and Mental Health.

Refurbishing of acpjc.org

Each year the content of the online version of *ACP Journal Club* (acpjc.org) is updated. Abstracts and their accompanying commentaries are reviewed at 5-year intervals (e.g., content from 1992 and 1997 is updated in 2002). The reviews are done by the editor and associate editors of the journal, the author of the original article, the commentator, and a research associate familiar with study design and biostatistics. Outdated studies are archived, and the remaining reports are updated, if necessary. Updates could include revisions to the title of the abstract, additions to the commentary, the addition of a table to the abstract and possibly the calculation of more clinically useful statistics (e.g., number needed to treat), and links to other relevant studies in the database.

Reference

1. **Haynes RB, Mulrow CD, Huth EJ, Altman DG, Gardner MJ.** More informative abstracts revisited. Ann Intern Med. 1990;113:69-76.

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TERMS USED IN THERAPEUTICS

Allocation concealed: The authors were deemed to have taken adequate measures to conceal allocation to study groups from those responsible for assessing patients for entry in the trial (e.g., central randomization; sequentially numbered, opaque, sealed envelopes; sealed envelopes from a closed bag; numbered or coded bottles or containers; drugs prepared by the pharmacy; or other descriptions convincing of concealment).

Allocation not concealed: The authors were deemed not to have taken adequate measures to conceal allocation to study groups from those responsible for assessing patients for entry in the trial (e.g., no concealment procedure, sealed envelopes that were not opaque, or other descriptions not convincing of concealment).

Unclear allocation concealment: The authors did not report or provide a description of allocation concealment that allowed for classification as concealed or not concealed.

Blinded: Any or all of the clinicians, patients or participants, outcome assessors, or statisticians were unaware of who received which study intervention. Those who are blinded are indicated in parentheses. If "initially" is indicated (e.g., blinded [patients and outcome assessor initially]), the code was broken during the trial, for instance, because of adverse effects.

Blinded (unclear): The authors did not report or provide us with an indication of who, if anyone, was unaware of who received which study intervention.

Unblinded: All participants in the trial (clinicians, patients or participants, outcome assessors, and statisticians) were aware of who received which study intervention.

DEFINITIONS RELATING TO DATA PRESENTATION IN THERAPEUTICS

1. The experimental treatment reduces the risk for a bad event:

RRR (relative risk reduction): the proportional reduction in rates of bad events between experimental (experimental event rate [EER]) and control (control event rate [CER]) patients in a trial, calculated as |EER – CER|/CER and accompanied by a 95% confidence interval (CI).

ARR (absolute risk reduction): the absolute arithmetic difference in event rates, |EER – CER|.

NNT (number needed to treat): the number of patients who need to be treated to prevent 1 additional bad outcome; calculated as 1/ARR, rounded up to the next highest whole number, and accompanied by its 95% CI.

2. The experimental treatment increases the probability of a good event:

RBI (relative benefit increase): the increase in the rates of good events, comparing experimental and control patients in a trial, also calculated as |EER – CER|/CER.

ABI (absolute benefit increase): the absolute arithmetic difference in event rates, |EER – CER|.

NNT: calculated as 1/ABI; denotes the number of patients who must receive the experimental treatment to create 1 additional improved outcome in comparison with the control treatment.

3. The experimental treatment increases the probability of a bad event:

RRI (relative risk increase): the increase in rates of bad events, comparing experimental patients to control patients in a trial, and calculated as for RBI. RRI is also used in assessing the effect of risk factors for disease.

ARI (absolute risk increase): the absolute difference in rates of bad events, when the experimental treatment harms more patients than the control treatment; calculated as for ABI.

NNH (number needed to harm): the number of patients who, if they received the experimental treatment, would lead to 1 additional person being harmed compared with patients who receive the control treatment; calculated as 1/ARI.

Confidence interval (CI): the CI quantifies the uncertainty in measurement; usually reported as 95% CI, which is the range of values within which we can be 95% sure that the true value for the whole population lies.

Weighted event rates: the contributions of individual studies to the total in a meta-analysis, determined by the sample size and the number of events in each study.

TERMS USED IN DIAGNOSIS

Sensitivity: the proportion of patients with the target disorder who have a positive test result (a/[a + c]) (Figure).

Specificity: the proportion of patients without the target disorder who have a negative test result (d/[b + d]) (Figure).

Pretest probability (prevalence): the proportion of patients who have the target disorder, as determined before the test is carried out ([a + c]/[a + b + c + d]) (Figure).

Pretest odds: the odds that the patient has the target disorder before the test is carried out (pretest probability/[1 – pretest probability]).

Likelihood ratio (LR): the ratio of the probability of a test result among patients with the target disorder to the probability of that same test result among patients who are free of the target disorder. The LR for a positive test (positive likelihood ratio) is calculated as sensitivity/(1 – specificity). The LR for a negative test (negative likelihood ratio) is calculated as (1 – sensitivity)/specificity.

Post-test odds: the odds that the patient has the target disorder after the test is carried out (pretest odds × LR).

Post-test probability: the proportion of patients with that particular test result who have the target disorder (post-test odds/[1 + post-test odds]). Use of a nomogram avoids the need for these calculations.

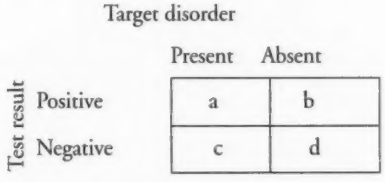
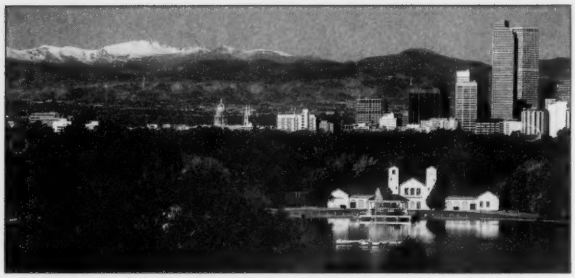


Figure. Comparison of test results with a diagnostic standard.



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- Vision, initiative, and innovation. Has a clear vision for the future of ambulatory care, including implementing the chronic disease management model and understanding the role of electronic medical records in delivering evidence-based primary care, and has demonstrated innovation and initiative in realizing that vision.
- Project management and teamwork. Has overseen and led complex projects and coordinated interdisciplinary teams.
- Quality improvement. Understands principles of quality improvement and has experience in implementing and monitoring QI programs.
- Supervision and mentoring. Has significant experience in supervising and mentoring others.
- Organizational and political savvy. Has experience successfully navigating in large organizations.

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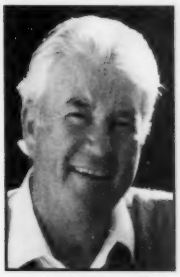

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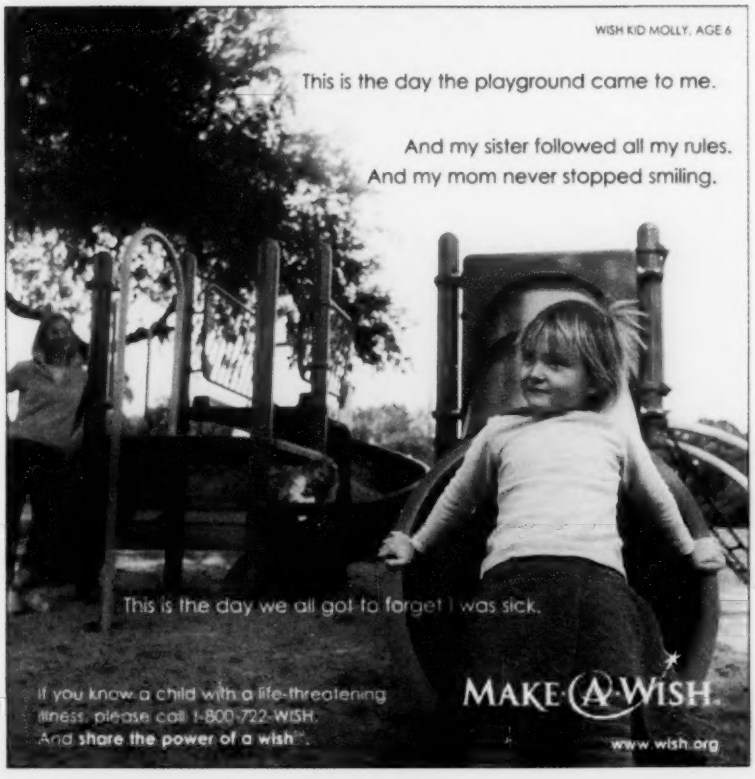
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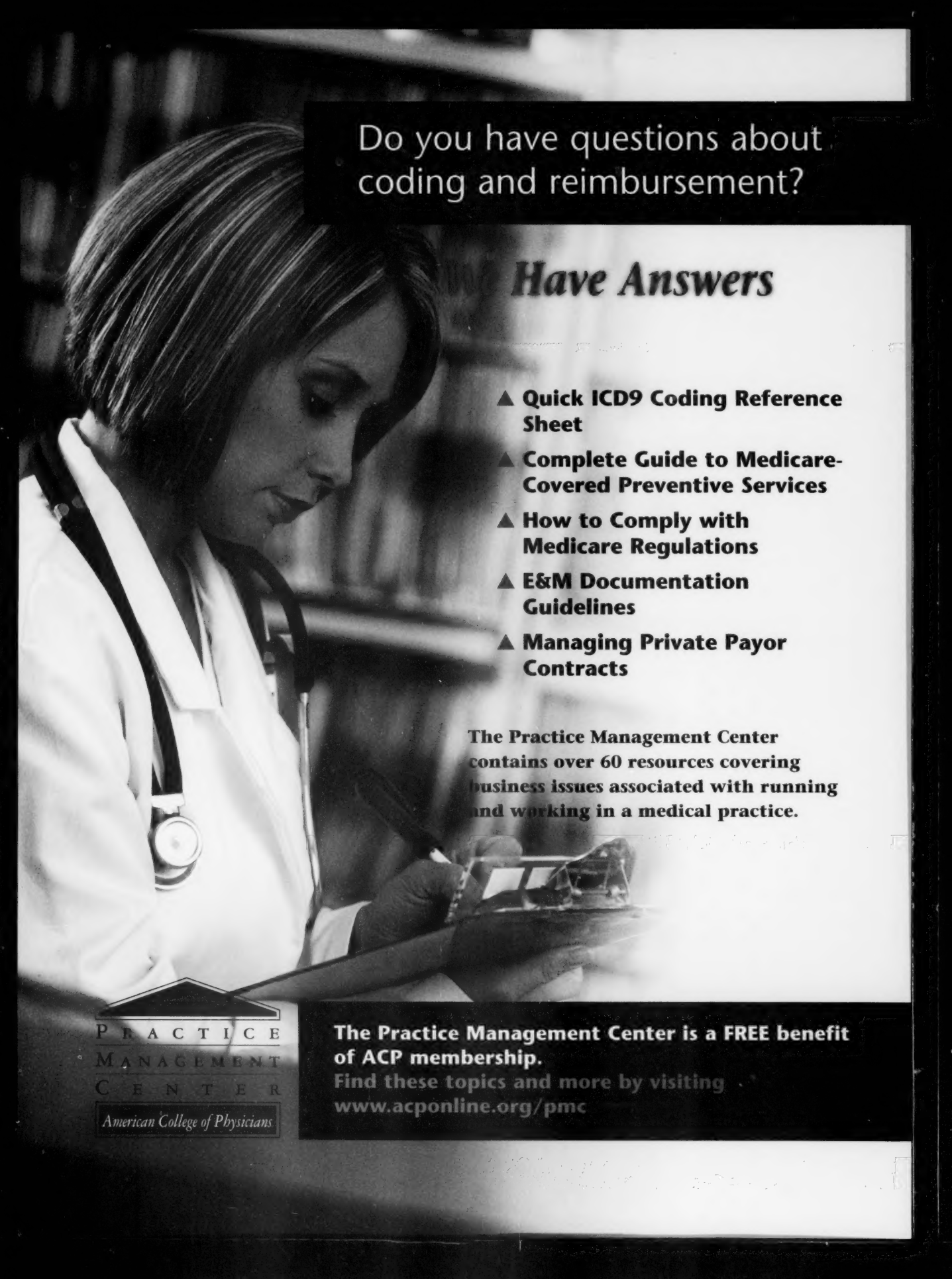
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